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EDITORIAL · REDAKSIONEEL

COXSACKIE VIRUS MYOCARDITIS OF THE NEWBORN

A HIGHLY FATAL VIRUS DOSE

We devote this issue of the journal to a considerable, very comprehensive and important report on two outbreaks of Coxsackie virus myocarditis of the newborn which occurred in Cape Town in April and in June 1957.* The episodes have been studied intensively from the clinical, pathological, virological and epidemiological points of view, valuable diagnostic and prophylactic measures being suggested by the various authors. The outbreak also made possible a very full description of the evolution of the myocardial lesions and provided evidence of the rapidity of repair—an extremely interesting observation.

The findings of the Cape Town investigatiors clinch beyond any reasonable doubt the cause of the disease as due to the Coxsackie virus, a virus perhaps better known as the aetiological agent of Bornholm disease (the devil's grip, epidemic pleurodynia, etc.).

Myocarditis neonatorum may have many causes. Our appreciation of the significance of the Coxsackie virus in this connexion is, however, recent and entirely due to the original contribution made by South African practitioners.

* A general review of *The Coxsackie Virus Infections*, by Dr. G. Selzer, was published in this Journal on 3 May 1958, pp. 219–222.

COXSACKIE-VIRUS-HARTSPIERONTSTEKING BY PASGEBORENES

'N HOOGS NOODLOTTIGE VIRUS-SIEKTE

Hierdie uitgawe van *Mediese Bydraes* word gewy aan 'n omvangryke, baie omvattende en belangrike verslag oor die twee uitbrekings van Coxsackie-virus-hartspierontsteking onder pasgeborenes wat in April en Junie 1957 in Kaapstad voorgekom het.* Die episodes is intensief uit 'n kliniese, patologiese, virologiese en epidemiologiese standpunt bestudeer, en verskillende bydraers doen waardevolle diagnostiese en profilaktiese voorsorgsmaatreëls aan die hand. Die uitbreking het ook 'n baie volledige beskrywing van die ontwikkeling van die hartspierletsels moontlik gemaak, en bewys van die herstel-snelheid opgelewer—'n buitengewoon interessante waarneming.

Die bevindings van die Kaapstadse ondersoekers bewys bo alle redelike twyfel dat die siekte veroorsaak is deur die Coxsackie-virus, 'n virus wat waarskynlik beter bekend is as die etiologiese oorsaak van Bornholm se siekte (duiwelsgreep, epidemiese pleurodinie, ens.).

Hartspierontsteking onder pasgeborenes kan etlike oorsake hê. Ons kennis van die betekenisvolle rol wat die Coxsackie-virus in hierdie verband speel, is pas onlangs ingewin, en moet ge-

* 'n Algemene oorsig van die Coxsackie-virus-infeksies deur dr. G. Selzer is op 3 Mei 1958 in hierdie Tydskrif gepubliseer (bl. 219–222).

When in 1956 the report became available of the first cases (in Johannesburg in 1952) in which Coxsackie virus was incriminated by Javett, Heymann *et al.* as the cause of the outbreak,[1] Sabin (a most distinguished virologist) expressed a rather scathing scepticism about the South African suggestion. He felt that the evidence did not establish the Coxsackie virus as the cause of the myocarditis and denied that the outbreak in the 10 children reported on was even significantly associated with Coxsackie infection.[2] Within about a year, however, Sabin abandoned his objections[3] in the light of further evidence which had accumulated and which vindicated fully the original claim advanced by Javett, Heymann *et al.*, a claim which clearly established a new and important cause of myocarditis in the newborn.

Coxsackie myocarditis neonatorum may occur sporadically and, in its epidemic form, may easily be overlooked. In the 1952 Johannesburg outbreak (which, incidentally, occurred at a time when Bornholm disease was prevalent in that city) the maternity home authorities were totally unaware that a disastrous communicable disease was 'raging in their nursery.'[1] This was because some of the children sickened at home a few days after their discharge from the maternity hospital.

Indeed, it was due to the clinical acumen of Dr. S. N. Javett that the epidemic significance of what was happening was recognized, with the result that the local health authorities were immediately alerted and investigations instigated which resulted in an important discovery. Gear and Measroch[4] isolated the Coxsackie virus in stools of cases from this epidemic and subsequently the virus was demonstrated in the myocardium of a fatal case,[1] unconnected with the 1952 epidemic.

Suckling and Vogelpoel stress elsewhere in this issue that the early diagnosis of Coxsackie myocarditis is most difficult. But an awareness of the possibility must always be in the mind of the alert clinician, especially when Bornholm disease is about in the community. The heel en al toegeskryf word aan die bydraes van Suid-Afrikaanse praktisyns.

In 1956 is 'n verslag gepubliseer oor die eerste gevalle (in Johannesburg in 1952) waar die Coxsackie-virus deur Javett, Heymann *et al.* as die oorsaak van die uitbreking aangewys is. Destyds het Sabin, 'n baie vooraanstaande viroloog, hom met vlymende skeptisisme oor die Suid-Afrikaanse suggestie uitgelaat. Hy het gemeen dat die getuienis nie afdoende beyws het dat die Coxsackie-virus die oorsaak van die hartspierontsteking was nie, en het ontken dat die uitbreking by die 10 kinders waaroor daar toentertyd verslag gedoen is, selfs in die verste verte met Coxsackie-infeksie in verband gebring kon word.[2] Binne 'n jaar, egter, het Sabin sy besware laat vaar[3] in die lig van verdere getuienis wat ingewin is en die oorspronklike aanspraak van Javett, Heymann *et al.* gestaaf het—'n aanspraak wat 'n nuwe en belangrike oorsaak van hartspierontsteking by pasgeborenes aangewys het.

Coxsackie-virus-hartspierontsteking by pasgeborenes kan sporadies voorkom, en, in sy epidemiese vorm, kan dit maklik oor die hoof gesien word. Tydens die 1952-uitbreking in Johannesburg (wat, tussen hakies, voorgekom het op 'n tydstip toe Bornholm-siekte baie algemeen in daardie stad was) was die owerheid van die kraaminrigting volkome onbewus van die feit dat 'n dodelike oordraagbare siekte ‚in hul kinderkamer gewoed het.'[1] Dit was omdat 'n paar van die kinders siek geword het by die huis—'n paar dae ná hul ontslag uit die kraaminrigting.

Trouens, dit was aan die kliniese skerpsinnigheid van dr. S. N. Javett te danke dat die epidemiese betekenis van die gebeure herken is. Ten gevolge hiervan is die plaaslike gesondheidsowerheid onmiddellik op sy hoede gestel, en ondersoek is gedoen wat op 'n belangrike ontdekking uitgeloop het. Gear en Measroch[4] het die Coxsackie-virus in die ontlasting van kinders wat by hierdie epidemie betrokke was. afgesonder, en later is die virus ook gevind in die hartspier van 'n noodlottige geval[1] wat nie tydens die 1952-epidemie aangesteek het nie.

1. Javett, S. N., Heymann, S., Mundel, B., Pepler, W. J., Lurie, H. I., Gear, J. H. S., Measroch, V. and Kirsch, Z. (1956): J. Pediat., **48**, 1.
2. Sabin, A. B. (1956–1957): *Year Book of Pediatrics*, p. 268. Chicago: The Year Book Publishers, Inc.
3. Sabin, A. B. (1957–58): *Year Book of Pediatrics*, p. 269. Chicago: The Year Book Publishers Inc.
4. Gear, J. and Measroch, V. (1953): *S.A.I.M.R. Annual Report for 1952*, pp. 38–39.

1. Javett, S. N., Heymann, S., Mundel, B., Pepler, W. J., Lurie, H. J., Gear, J., Measroch, V. en Kirsch, Z. (1956): J. Pediat., **48**, 1.
2. Sabin, A. B. (1956-1957): *Year Book of Pediatrics*, bl. 268. Chicago: The Year Book Publishers, Inc.
3. Sabin, A. B. (1957–1958): *Year Book of Pediatrics*, bl. 269. Chicago: The Year Book Publishers, Inc.
4. Gear, J. en Measroch, V. (1953): *S.A.I.M.N., Jaarverslag vir 1952*, bl. 38–39.

heart is often the target-organ bearing the fatal brunt of the attack, and although no specific therapy is as yet available, early treatment, indeed from the moment the diagnosis is suspected, and specially directed to sustaining the heart, may be life-saving.

The mode of infection appears to be airborne. Infection should therefore be preventable. Certainly any case of suspected maternal Bornholm disease should be excluded from maternity homes and precautions (especially about visitors) should be particularly rigid when Coxsackie infection of any type is current. The abandonment of the common nursery and the retention of the new born infant with its mother are some of the valuable suggestions made by Kipps *et al.* elsewhere in this issue. Indeed, in such circumstances, there is much to be said for encouraging delivery at home and avoiding at all costs a nursing home which may be the reservoir of a fatal infection. The infection disseminated in a nursing home constitutes a major disaster because of the high neonatal mortality rate.

Not all cases are fatal, and the prognosis for the child who recovers is good. Although the comprehensive studies reported in this issue indicate how severe the myocardial lesion can be, there is every reason to believe that the heart will clinically be restored completely to normal. All the damage appears to occur at the time of the illness and there is no question of repeated damaging attacks.

The medico-legal implications of this new disease are very considerable. The viraemia may overwhelm an apparently healthy infant in a few hours. A child put to sleep perfectly well after its last feed, may be found dead the next morning and at autopsy very little, if anything, may be seen to account for the fatal outcome.

In recent years there has been increasing scepticism of the extensive role formerly assigned to overlaying as a cause of death of helpless babies.[5] In Coxsackie myocarditis of the newborn we have an important and easily overlooked explanation of death from natural causes which should be appreciated by the pathologist performing an autopsy.

The symposium on Coxsackie virus myocarditis of the newborn, to which this issue is devoted, marks an outstanding contribution of world-wide significance to the practice of medicine by South African investigators.

5. Bowden, K. M. (1953): J. Forensic Med., **1**, 19.

Elders in hierdie uitgawe lê Suckling en Vogelpoel klem daarop dat die vroeë diagnose van Coxsackie-virus-hartspierontsteking besonder moeilik is. Maar hierdie moontlikheid moet altyd in gedagte gehou word deur die wakkere klinis, veral as Bornholm-siekte in 'n gemeenskap voorkom. Die hart is dikwels die teikenorgaan wat die spit van die noodlottige aanval moet afbyt, en hoewel spesifieke terapie nog nie beskikbaar is nie, kan vroeë behandeling wat toegepas moet word vanaf die oomblik dat die geneesheer hartspierontsteking vermoed, en spesiaal op die onderskraging van die hart toegespits moet word, die lewe van die suigeling red.

Dit skyn asof dit 'n luggedraagde infeksie is. Dit behoort derhalwe moontlik te wees om dit te voorkom. In elk geval behoort 'n moeder wat aan verdagte Bornholm-siekte ly beslis nie tot 'n kraaminrigting toegelaat te word nie, en voorsorgmaatreëls (veral vir sover dit besoekers betref) moet baie streng toegepas word as Coxsackie-infeksie van hoegenaamd enige soort algemeen is. Die nie-gebruik van die gesamentlike kinderkamer en die beperking van die pasgebore suigeling tot sy moeder ressorteer onder die waardevolle wenke wat elders in hierdie uitgawe deur Kipps *et al.* aan die hand gedoen word. Trouens, in sulke omstandighede kan daar veel gesê word ten gunste van verlossing by die huis en die vermyding tot elke prys van 'n kraaminrigting wat die bron van noodlottige infeksie kan word. Die infeksie wat in 'n kraaminrigting versprei word, is 'n eersterangse ramp, weens die hoë sterftesfyer wat dit onder pasgeborenes teweeg kan bring.

Nie alle gevalle is noodlottig nie, en die prognose vir die kind wat herstel, is goed. Hoewel die omvattende studies waaroor daar in hierdie uitgawe verslag gedoen word, 'n aanduiding gee van hoe ernstig die hartspierlestel kan wees, is daar alle rede om aan te neem dat die hart klinies volkome tot normaal sal herstel. Al die skade skyn aangerig te word ten tyde van die siekte, en daar is geen kwessie van herhaaldelike beskadigingsaanvalle nie.

Die medies-regskundige implikasies van hierdie nuwe siekte is aansienlik. Die viraemie kan 'n blykbaar gesonde suigeling binne 'n paar uur oorweldig. 'n Kind wat volkome gesond aan die slaap raak na sy laaste voeding, kan die volgende môre dood aangetref word, en die lykskouing kan min, indien enigiets, oplewer om te verduidelik waarom die kind gesterf het.

In die afgelope jare is daar alhoemeer skeptisisme uitgespreek oor die groot rol wat doodlê vroeër sou gespeel het as 'n oorsaak van sterfgevalle onder hulpelose babetjies.[5] Coxsackie-virus-hartspierontsteking onder pasgeborenes verstrek 'n belangrike verduideliking (wat maklik oor die hoof gesien kan word) van sterfgevalle ten gevolge van 'n natuurlike oorsaak wat in gedagte gehou behoort te word deur die patoloog wat 'n lykskouing uitvoer.

Die simposium oor Coxsackie-virus-hartspierontsteking onder pasgeborenes waaraan hierdie uitgawe gewy is, is 'n vortreflike bydrae van wêreldwye betekenis tot die geneeskunde deur Suid-Afrikaanse ondersoekers.

5. Bowden, K. M. (1953): J. Forensic Med., **1**, 19.

COXSACKIE MYOCARDITIS OF THE NEWBORN

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We report here on 8 of the 9 cases of Coxsackie B3 myocarditis in newborn European infants, occurring in 2 outbreaks on the upper floor of one nursing home in Cape Town. There were 6 cases in the first outbreak in April 1957, and 2 were seen by us in the second, in June. Three of the first 6 cases died and one of the other 2, giving a 50% mortality of the cases in our care. In all those who died, the virus was cultivated from the myocardium, and from the stools of all those who recovered.

The subject of virus myocarditis has recently been reviewed.[1, 2] These accounts mention the various types of myocarditis repeatedly demonstrated in animals, including Coxsackie B3 myocarditis in cortisone-treated mice. Criteria of proof are laid down, emphasizing the isolation of the causal agent from affected tissues and its recovery in similar circumstances from like cases. Clinical findings in Man are listed, including fever with disproportionate tachycardia, triple rhythms of the heart, cyanosis, dyspnoea, hepatomegaly and oedema, pallor, listlessness and vomiting, electrocardiographic changes and radiological evidence of cardiac enlargement. Histological studies reveal the presence of myocarditis.

Montgomery *et al.*[3] in Rhodesia, and Javett *et al.*[4] in Johannesburg have recorded outbreaks of myocarditis in the newborn human, in which the Coxsackie virus has been recovered from some or all of the cases, but not from the myocardium, except in one case presented by Javett *et al.*[4] in an additional note, but not occurring in the epidemic described. One case with meningo-encephalitis was reported[5] in which the virus was recovered from the spinal cord, but not from the myocardium, although the histological features of myocarditis were present. Four fatal cases were described[6] in which Coxsackie B4 virus was isolated from the myocardium. This series would appear to be the second, in which proof of Coxsackie myocarditis has been obtained and the largest so far recorded.

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CASE REPORTS

Case I (Baby KAI) Male. This baby, the first of his parents, was born by the vertex at full term 30 March 1957, after a normal pregnancy and labour. The baby weighed 7 lb. 15 oz. (3,600 g.) and was 21½ inches (55 cm.) long. His mother was 22 years old, and became febrile with a headache on the second day of the puerperium. She had further spikes of fever (to 99.8° F.) on the fourth and seventh days, but no more until her return home on the tenth day. Shortly after that she had a temperature of 103° F. on one occasion.

The baby thrived normally until 6 April 1957, when he weighed 7 lb. 11 oz. (3,487 g.), and was being fed on a cow's milk mixture. On 7 April his temperature rose to 101° F. rectally, and his doctor found only some redness of the throat. He had vomited twice, but his stools were normal. The next day his temperature was 102° F., and he was put on Ilotycin 25 mg. 6-hourly. In 24 hours the temperature was normal and did not rise again (Fig. 1).

Feeding was continued by bottle with cow's milk, and he was seen in consultation on 10 April because he was refusing his feeds and looking ill.

Examination showed a dyspnoeic, cyanotic infant with a normal temperature and a pulse rate of 140 per minute. Cardiomegaly was not detected clinically, or any sign of pulmonary disease. There were no cardiac murmurs and the liver and spleen were not enlarged. The fontanelle was normal and there was no neck rigidity. X-ray of the chest (portable at 33 inches) showed a doubtful left upper lobe pneumonia and a possible cardiomegaly. The transverse diameter of the heart was 6.7 cm. and the cardio-thoracic index 0.62.[7] Lumbar puncture was performed, and crystal clear fluid obtained; it was not further examined.

The baby was placed in an oxygen tent, where he became bright pink, having been previously deeply cyanosed. This was thought to be unlike congenital heart disease with a right-to-left shunt, or methaemoglobinaemia.

At this stage the diagnosis was considered to be pneumonia, and Chloromycetin palmitate 1 drachm (125 mg.) was given 8-hourly.

The following morning he became much worse and cyanotic, while still in the oxygen tent. His liver was now enlarged to 3 fingers' breadth, and he was oedematous. The lungs were full of moist crepitations. X-ray of the chest showed that the transverse diameter of the heart was still at 6.7 cm., but that the cardiothoracic index had increased to 0.67. The diagnosis was changed to myocarditis, probably of virus origin, and Digitalis Folium was begun in a dose of ¼ gr. 8-hourly. Mersalyl ½ ml. was given by injection. His condition continued to deteriorate, and he died the same afternoon. At necropsy the following day, myocarditis was found on frozen section and the virus was later isolated from the myocardium.

Case II (*Baby STE*) Male. This baby, the first of his parents, was born by the vertex at full term on 2 April 1957 after a normal pregnancy and labour. He weighed 7 lb. 5 oz. (3,317 g.) and was 20½ inches (52 cm.) long. His mother was 27 years old, and became febrile 2 days after delivery, and again on the fifth and seventh days of the puerperium. On the last occasion she was given penicillin.

The baby thrived until 7 April, when he weighed 6 lb. 15 oz. (3,147 g.). He was fed at the breast with a 50% cow's milk complement. On 8 April he developed a temperature of 101° F. rectally and was found to have a red throat. He had not vomited and the stools were normal. On 11 April, in view of the continuing fever, polycycline 25 mg. 6-hourly

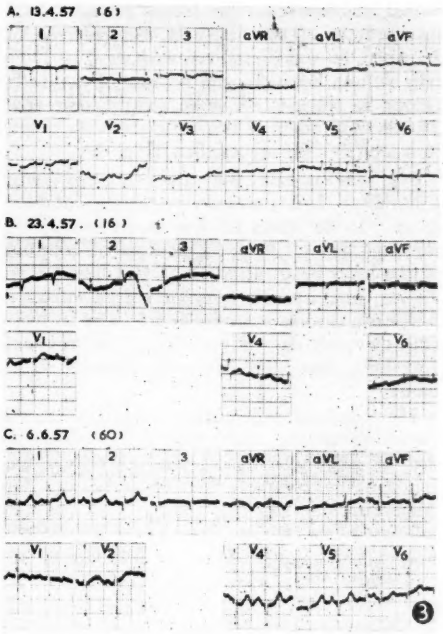


Fig. 3. Electrocardiograms (Case II). The details are shown in Table II and in the text. In this, and in subsequent electrocardiograms, both the date and the day of the illness are noted (in brackets) on each graph.

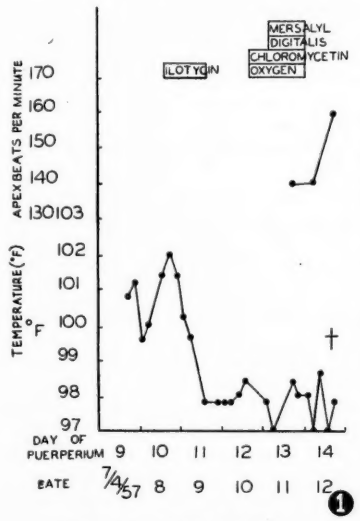


Fig. 1. Case I (Baby KAI).

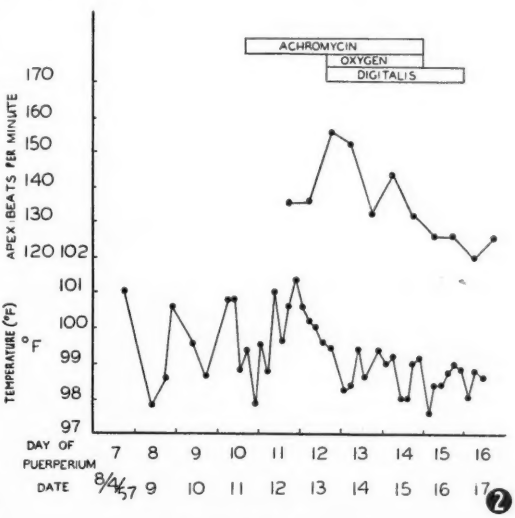


Fig. 2. Case II (Baby STE).

was given by mouth. He was seen in consultation on 12 April when his temperature was 101° F., and his heart rate 136 per minute. When the report on the frozen section of the myocardium of the first case was received on 13 April, he was digitalized with gr. ¼ of Digitalis Folium 8-hourly, and because of his dusky colour he was placed in an oxygen tent (Fig. 2). An ECG taken at this time showed changes in keeping with myocarditis (Fig. 3A).

He was nursed flat and tube-fed, with Chloral gr. 1 as necessary to secure complete quiet. In 48 hours he was much better, and the digitalis was stopped, because of coupling of the heart beats, after 2¼ gr. had been given. At no time was his liver or spleen enlarged, nor was a cardiac murmur heard. On 18 April (the eleventh day of his illness) he was well and fully bottle-fed, and was allowed to go home.

He remained well until 21 April, when his breathing became rapid and, on the following day, he was seen again, when his liver was found to be 2 fingers' breadth enlarged. His heart rate was 140 per minute, with no murmurs or triple rhythm. He was re-admitted to hospital and given Digoxin 0.125 mg. *b.d.* His white blood cell count was 27,600 per c.m. with 59% polymorphonuclear cells and 37% lymphocytes. Oxygen was given and 0.1 ml. Mersalyl. The next morning he was much better and his liver was no longer enlarged. X-ray of the heart showed a cardiothoracic index of 0.64, which was considered normal in the supine position. An ECG was found to be within normal limits, though the QRS and T voltage was still low (Fig 3B).

From then on his progress has been satisfactory and he was seen again on 5 June 1957, weighing 10½ lb. (4,763 g.). His ECG (Fig. 3C) and chest X-ray showed no abnormality.

Coxsackie B3 virus was isolated from the stool.

He was seen again on 3 February 1958 weighing 28 lb. and very well, without abnormal physical signs.

Case III (*Baby TRI*) *Female.* This baby, the second of her parents, was born on 6 April 1957 by the vertex at full term after a normal pregnancy and labour. She weighed 6 lb. 6 oz. (2,891 g.) and was 20½ inches (52 cm.) long. Her mother was 29 years old, and was apyrexial throughout the relevant period, but developed a coryza on 21 April. The sib has remained well.

The baby thrived normally until 10 April, when she weighed 6 lb. 4 oz. (2,835 g.), and was fully breast-fed. On 11 April she ran a temperature of 101° F. rectally and on examination she was limp and moaning with a tachycardia, of 150 per minute and some reddening of the throat. She had not vomited and the stools were normal. Chloromycetin palmitate was begun in a dose of ½ drachm (62.5 mg.) 6-hourly, and as soon as the report on Case I was received, digitalis ¼ gr. 8-hourly was added (Fig. 4). The baby was nursed flat and tube-fed with Chloral gr. 1, as necessary, to control restlessness.

On 15 April her condition was deteriorating. She was limp, her colour had become dusky and she was vomiting. Thrush was present in the mouth for which Nystatin was given. Oxygen therapy was begun. The liver, however, did not enlarge at this or at any other time, nor was a cardiac murmur or triple rhythm ever detected. There was no oedema.

Because of the vomiting and the possibility of inhalation, Chloromycetin was recommenced. Her condition remained critical for the next 3 days, but by 18 April her colour had improved, and the child appeared more lively with improved muscle tone.

Since the excretion of digitalis is slow, and with the possibility in mind that the vomiting had been a toxic effect, the digitalis was stopped on 17 April, when 2¾ gr. had been given in all. After the unexpected death of Case IV, an ECG was taken on 22 April. This showed minimal S-T elevation in V4 and V6 suggestive of epicardial damage (Fig. 5A). By 1 May 1957 the graph had returned to within normal limits, although the amplitude of the T waves was still low (Fig. 5B).

It will be seen from Fig. 4 that there were 5 pyrexial phases, the most serious being the second and third. Bottle feeding was resumed on 19 April with breast milk, complemented with a 50% cow's milk mixture.

She was discharged from hospital on 3 May 1957.

She was seen again in June 1957 with a normal X-ray of the chest, and more recently on 19 July 1957, when she weighed 12 lb. 13 oz. (5,812 g.) and was a normally developed child with no signs of disease.

Coxsackie virus B3 was isolated from the stool.

Case IV (*Baby BRI*) *Female.* This baby, the second of her parents, was born by the vertex at full term on 4 April 1957, after a normal pregnancy and labour. The baby weighed 8 lb. 3 oz. (3,714 g.) and was 22½ inches (57 cm.) long. Her mother was 27 years old and for 2 days after delivery ran a temperature of 103° F., for which no cause was found. She remained well thereafter.

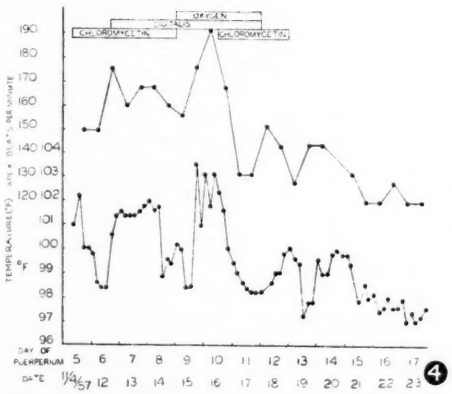


Fig. 4. Case III (Baby TRI).

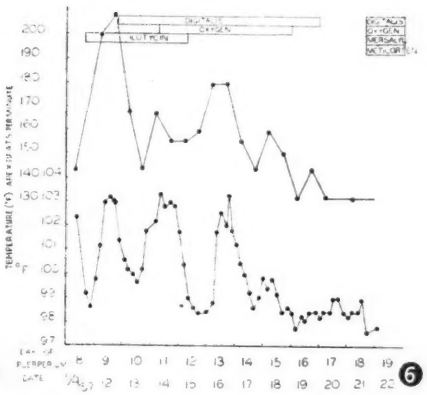


Fig. 6. Case IV (Baby BRI).

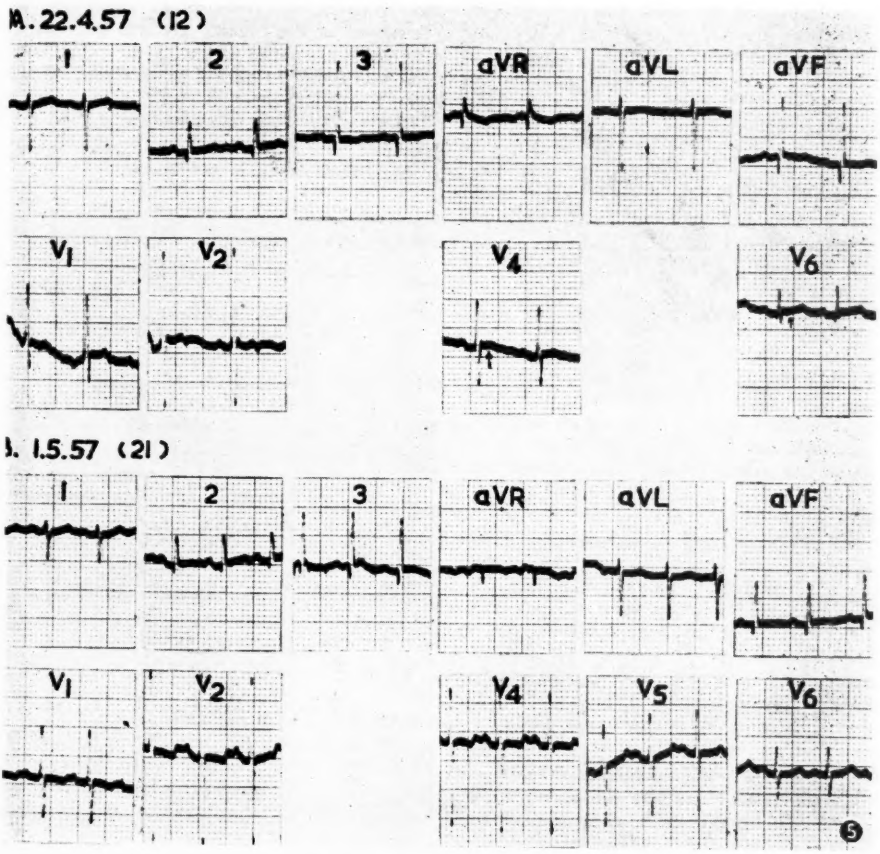


Fig. 5. Electrocardiograms. (Case III).

The baby thrived normally until 10 April, when she weighed 7 lb. 14 oz. (3,572 g.) and was being fed at the breast. On 11 April she ran a temperature of 102° F. rectally. There had been no vomiting and the stools were normal. The heart rate was 144 per minute, with some redness of the throat. There were no cardiac murmurs, no hepatomegaly and no oedema, but the child was not active. Ilotycin 25 mg. 6-hourly had been begun. On confirmation of the diagnosis in Case I, Digitalis Folium ¼ gr. 8-hourly had been begun. It was given for 3 days, and then ¼ gr. daily until 20 April (Fig. 6). The baby was nursed flat, and fed by tube with 50% human or cow's milk, as available. Chloral gr. 1 was given, as necessary, to ensure complete quiet.

She was very ill on the third day of her disease, vomiting and lying immobile in her cot with an ashen colour. There was no cardiac murmur and the liver was not enlarged Oxygen was given over the next 4 days and by 19 April she was improving in activity and colour, though extrasystoles were heard on that day. Vomiting, however, remained troublesome, and was attributed to digitalis intoxication, in the absence of further evidence of congestive cardiac failure; digitalis was therefore stopped after 3¼ gr. had been given. Bottle feeding was resumed on 20 April and she took well and appeared normally active.

On 21 April a grade 2 systolic cardiac murmur was heard for the first time. It was audible in the whole praecordium but maximal at the apex. That evening the baby suddenly became cyanosed and dyspnoeic, and the liver enlarged to 2 fingers' breadth. The systolic murmur persisted and a triple rhythm was heard. No oedema was found, or crepitations in the lungs. Digitalis was again given with oxygen, Mersalyl and Meticorten, but the baby died early the next morning.

Coxsackie B3 virus was isolated from the myocardium.

Case V (Baby OLI) Male. This baby, the first of his parents, was born by the vertex at full term on 5 April 1957 after a normal pregnancy and labour. The baby weighed 7 lb. 7 oz. (3,374 g.) and was 20 inches (51 cm.) long. The mother was 26 years old and had spikes of fever to 99° F. on the first and eighth days of the puerperium.

He thrived normally until 11 April, when he weighed the same as at birth, and was being fed at the breast. He was seen on that day in view of the illness of the other babies and was found to have a rectal temperature of 99° F. with a heart rate of 208 per minute. There had been no vomiting and the stool was normal. The throat was reddened. Bilateral cephalhaematomata were present.

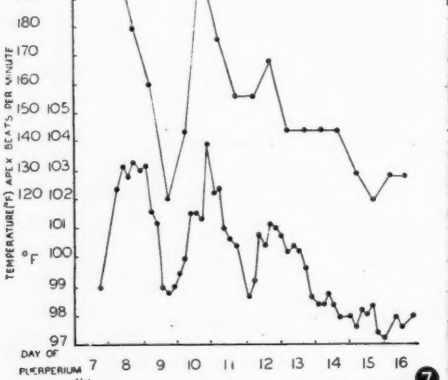


Fig. 7. Case V (Baby OLI).

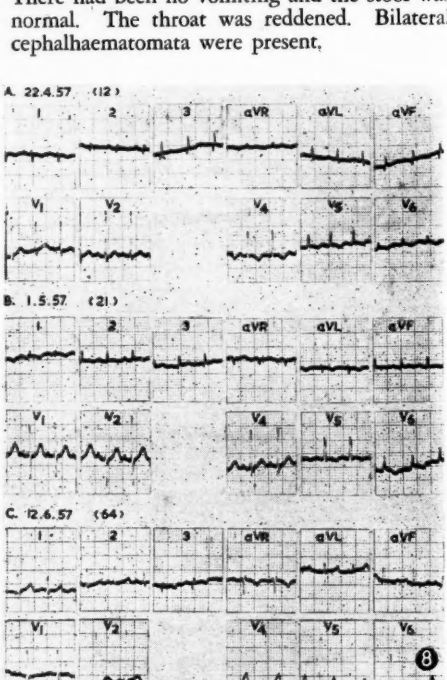


Fig. 8. Electrocardiograms (Case V).

Chloromycetin palmitate 40 minims (84 mg.) 8-hourly was begun, and the following day Digitalis Folium ¼ gr. 8-hourly. The digitalis was given for 3 days and continued thereafter in a dose of ¼ gr. daily until 13 April, 2¾ gr. being given in all (Fig. 7).

The baby was nursed flat and fed by tube with 20 oz. of 50% breast milk daily, with Chloral gr. 1 as necessary.

On 15 April, between the second and third relapses, the baby developed the duskiness seen in the other cases and became less active. Oxygen was given and by 17 April the baby was much improved, and bottle feeding was resumed 2 days later. The baby was discharged from hospital on 2 May 1957 well.

An ECG taken on 22 April, 4 days after stopping digitalis, showed low voltage and inversion of the T waves, in keeping with myocardial damage (Fig. 8A). Abnormal changes were still present on 1 May (Fig. 8B), but on 12 June the graph had returned to normal (Fig. 8C).

At no time were cardiac murmurs or triple rhythm heard; nor was the liver enlarged.

He was seen again in June 1957 with a normal X-ray of the chest and a normal ECG.

Coxsackie B3 virus was isolated from the stool.

Case VI (*Baby NOT*) *Male.* This baby, the third of his parents, was born by the vertex at full term on 7 April 1957 after a normal pregnancy and labour. The baby weighed 8 lb. 5 oz. (3,770 g.). The mother was aged 28 years and both were discharged home on 10 April. The mother was never ill.

The baby was seen at home on 14 April with a story of fever and sucking poorly for one day. There had been no vomiting and the stools were normal. The baby was ill, pale and dyspnoeic. The temperature was 98.8° F. rectally and the heart rate about 240 per minute with a triple rhythm. No oedema was found and the lungs were clear. The liver was enlarged 2½ fingers' breadth.

The baby was admitted to hospital with a diagnosis of acute myocarditis and died 4 hours later.

Coxsackie B3 virus was recovered from the myocardium.

One of the sibs, a male aged 2½ years, was taken ill on 16 April 1957 with a story of fever and upper abdominal pain for 3 days. He had vomited once.

He had a temperature of 105° F., with a heart rate of 160 per minute. Respiration was rapid and grunting, but there were no abnormal signs in the chest. The abdomen was soft and not tender, and the liver was not enlarged.

X-ray of the chest was normal and there were 5,000 while blood cells per c.mm.

A clinical diagnosis of Bornholm disease was made.

Case VII (*Baby HAE*) *Male.* This baby, the second of his parents, was born by the vertex at full term on 13 June 1957 after a normal pregnancy and labour. He weighed 7 lb. 14 oz. (3,572 g.) and was 21½ inches (55 cm.) long. His mother was 32 years old, of Swiss extraction, and on the fourth day of the puerperium developed a temperature of 100° F., with a headache and pain in both sides of the chest and in the epigastrium. On the following day the father also became ill with fever and right-sided chest pain, which recurred on and off for 5 days. The sib was not ill, but Coxsackie B3 virus was recovered from all their stools.

He thrived until 18 June 1957 when he weighed 7 lb. 8 oz. (3,402 g.) and was fully breast fed. The following day, 3 days after his mother's fever, his temperature rose to 100.2° F. rectally. He was seen on 20 June, when his temperature was 100.8° F. and his heart rate was 175 per minute. No vomiting had occurred and the stools were normal. The baby was limp and quiet. The throat was red and there was a hydrocoele of the right testis. The liver was palpable, one finger's breadth. There were no cardiac murmurs. X-ray of the heart was considered to be within normal limits. Serial X-rays are shown in Fig. 9. An ECG revealed minimal changes of doubtful significance (Fig. 10A), which would require serial ECG's for evaluation.

Because the parents' illnesses were so suggestive of Bornholm disease, it was decided to treat the child as a case of Coxsackie myocarditis. Digitalis Folium ¼ gr. 8-hourly was begun, and continued for 3 days, after which time it was reduced to ¼ gr. daily for the remainder of life. Oxygen was given and Chloromycetin palmitate 1 drachm (125 mg.) 8-hourly. The baby was nursed flat and tube fed with 4 feeds of 3 oz. 50% breast milk daily (Fig. 11).

The following morning the baby was a dusky colour and a grade 2 systolic murmur was audible over the whole praecordium, with a triple rhythm. The liver had become 2½ fingers' breadth enlarged. The lungs were clear and there was no oedema. X-ray showed a gross cardiomegaly (Fig. 9) and the ECG a nodal tachycardia (Fig. 10B). On the next day (22 June) the baby was much worse with

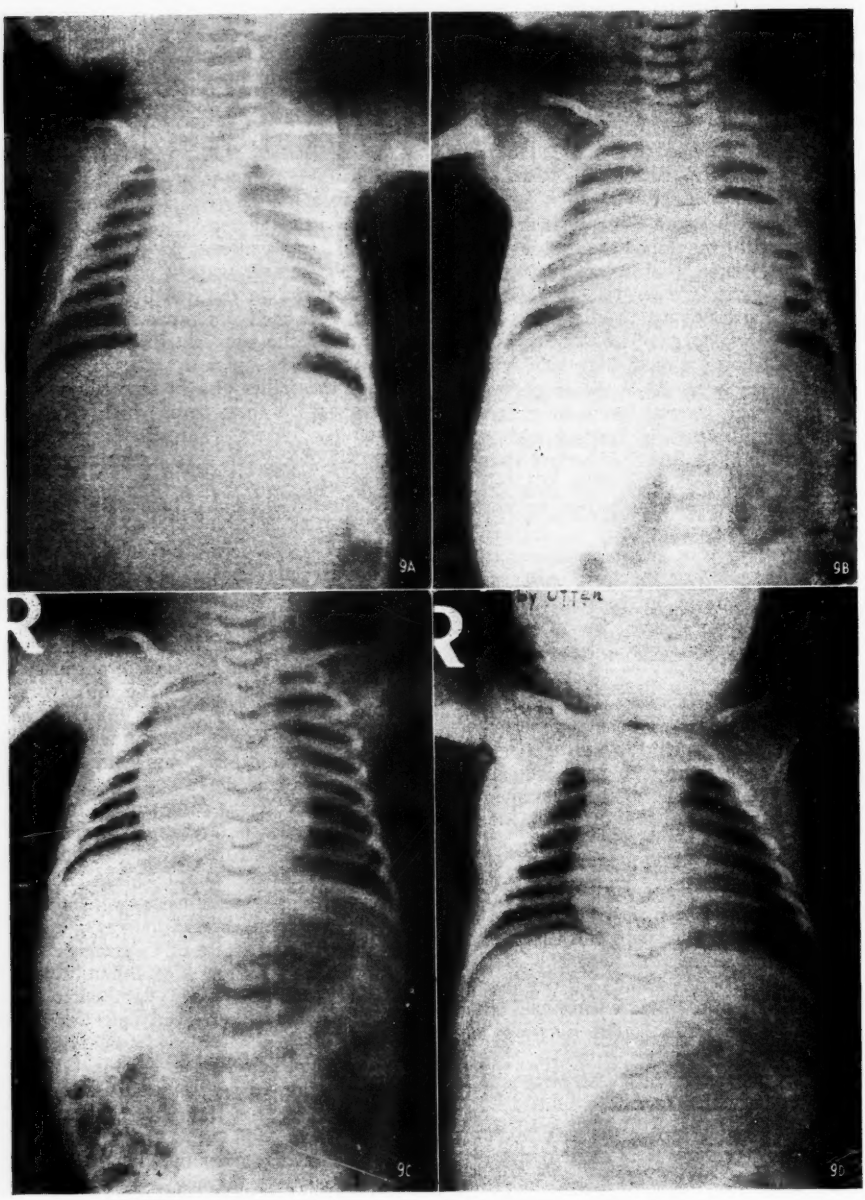


Fig. 9. Case VII. CTI: Cardio-Thoracic Index; CD: Cardiac Diameter (*Caffey* 1950)[7].
Fig. 9*a*. 20 June 1957 (2nd day of illness). CTI: 0·61; CD: 6·0 cm.
Fig. 9*b*. 22 June 1957 (4th day of illness). CTI: 0·70; CD: 7·0 cm.
Fig. 9*c*. 24 June 1957 (6th day of illness). CTI: 0·61; CD: 5·6 cm.
Fig. 9*d*. 27 June 1957 (9th day of illness). CTI: 0·57; CD: 5·3 cm.

marked dyspnoea and a respiratory rate of 112 per minute. On 23 June the triple rhythm had disappeared and so had the systolic murmur, but the heart rate was 160 per minute and the respiratory rate still 112 per minute. In the morning the baby passed a melaena stool and in the afternoon had a haematemesis followed by another melaena stool. This was thought to be associated with intestinal congestion but, in view of the low milk intake and the fact that the stools had become rather loose, 2.5 mg. vitamin K were given intramuscularly. Ascorbic acid 25 mg. was also added to the diet, and no further bleeding occurred. On 24 June the liver remained 2 fingers' breadth enlarged, but the systolic murmur had not recurred and was never heard again, not even just before death. The baby was still limp and grey. On 25 June the infant was better. The colour had improved and he was more active. The liver was just palpable. An ECG taken on 26 June revealed abnormal changes in all leads in keeping with widespread myocardial damage (Fig. 10C). He continued thus and then, on 27 June, the liver again enlarged to 2 fingers' breadth. At the same time the left parotid and sub-mandibular salivary glands swelled up. That night his colour became ashen and he died the following morning.

His weight was 7 lb. 8 oz. (3,402 g.) at the onset of the illness and despite the small intake of 12 oz. 50% breast milk daily, his weight was 7 lb. 3 oz. (3,260 g.) on 25 June, and 7 lb. 5 oz. (3,317 g.) on 27 June. This small loss and final gain may have been due to fluid retention, though no overt oedema was seen.

Coxsackie B3 virus was recovered from the myocardium.

Case VIII (Baby OFF) Male. This baby, the third of his parents, was born by the vertex at full time on 15 June after a normal pregnancy and labour. He weighed 8 lb. 2 oz. (3,685 g.) and was 22 inches (56 cm.) long. His mother was 27 years old and suffered no illness in the relevant period. The mother of Case VII used to visit this patient in her room, which she shared with another mother, whose baby escaped the disease.

The baby thrived normally until 21 June, when he weighed 8 lb. (3,629 g.). He was bottle-fed with a full-cream cow's milk mixture. The next day he developed a temperature of 101° F. rectally with a heart rate of 176 per minute, with frequent extra-systoles. The throat was slightly injected, otherwise nothing abnormal was found. In view of the known contact, treatment with Digitalis Folium was begun at once, and ¼ gr. 8-hourly was given for 3 days and thereafter ¼ gr. daily until 3 July 1957. At the same time Chloromycetin palmitate 1 drachm (125 mg.) 8-hourly was

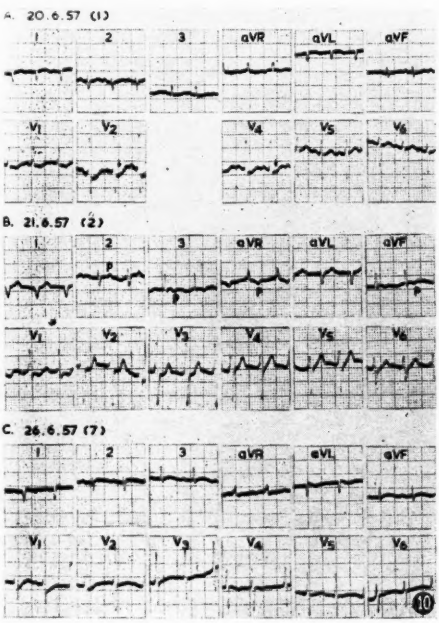


Fig. 10. Electrocardiograms (Case VII). The last tracing was recorded 2 days before death.

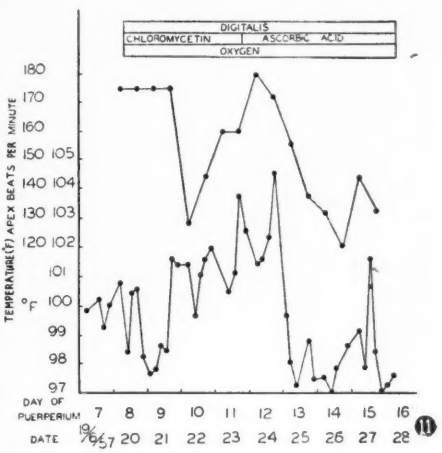


Fig. 11. Case VII (Baby HAE).

given, and the child nursed flat and tube fed with 4 feeds of 3 oz. 50% breast milk daily. Chloral gr. 1 was given, as necessary, to ensure complete quiet (Fig. 12).

An ECG taken on 22 June 1957 showed minimal changes of doubtful significance (Fig. 13A). X-ray revealed a heart of normal size (Fig. 14).

The following morning, 23 June, the heart rate was 176 per minute and frequent extrasystoles were heard, but no murmurs or triple rhythm. The liver was never enlarged nor was oedema found. The next day a grade 1 apical systolic murmur appeared, but no cardiomegaly could be seen on X-ray (Fig. 14). The colour had deteriorated and the baby was not so active, so oxygen was begun. Ascorbic acid 25 mg. daily was also added to the diet. The murmur had gone by the next evening, but re-appeared on 28 June and persisted until 1 July, after which it was not heard again.

The ECG taken on 26 June showed abnormal changes in keeping with myocarditis, but by 3 July the graph had returned to normal (Fig. 13B, C).

Despite the small feed the baby weighed 7 lb. 12½ oz. (3,517 g.) on 25 June and 7 lb. 15½ oz. (3,602 g.) on 27 June. He was discharged on 5 July and has remained well.

Coxsackie B3 virus was recovered from the stool.

He was seen again on 16 August and 14 December 1957 and is quite well.

COURSE OF THE DISEASE

The course of this illness is very unpredictable. Once the diagnosis is made, treatment should be continued until at least one week after the ECG has returned to normal (*vide* Case IV), and possibly digitalization should be prolonged until 6 weeks of age.

One of us (P. V. S.) has recently seen a baby 2 months old who died suddenly, and whose myocardium at autopsy showed hypertrophy of the left ventricle with extensive scattered areas of fibrosis possibly following Coxsackie myocarditis, though the virus was not recovered.

The most severe cases may be diagnosed by the presence of cardiac failure, circulatory failure or limpness and failure to suck within the first 2 days of the illness. Two of the 5 cases so assessed (Cases I and VI) died within 3 days of the onset of the symptoms in cardiac failure. Case VII went into cardiac failure on the third day of the illness, but survived on full treatment until the 10th day. Case IV, though very ill on the third day, was apparently on the mend and no longer receiving active treatment when she went into cardiac failure, while apyrexial, on the twelfth day and died within 24 hours. Case III was critically ill for some days but survived.

In general, the temperature charts show a relapsing course characteristic of Bornholm

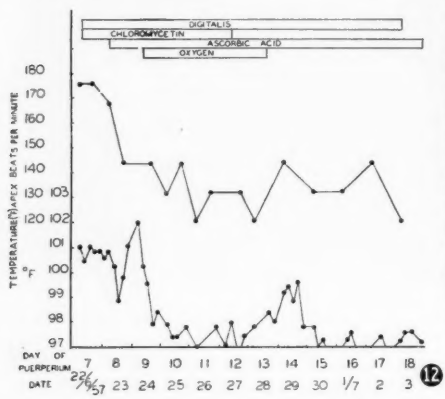


Fig. 12. Case VIII. (Baby OFF).

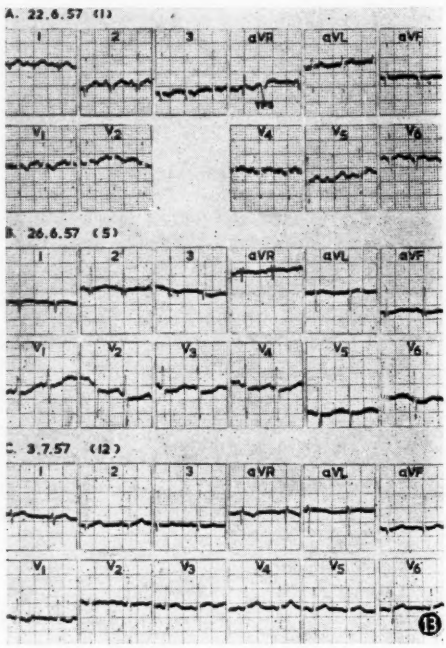


Fig. 13. Electrocardiograms (Case VIII).

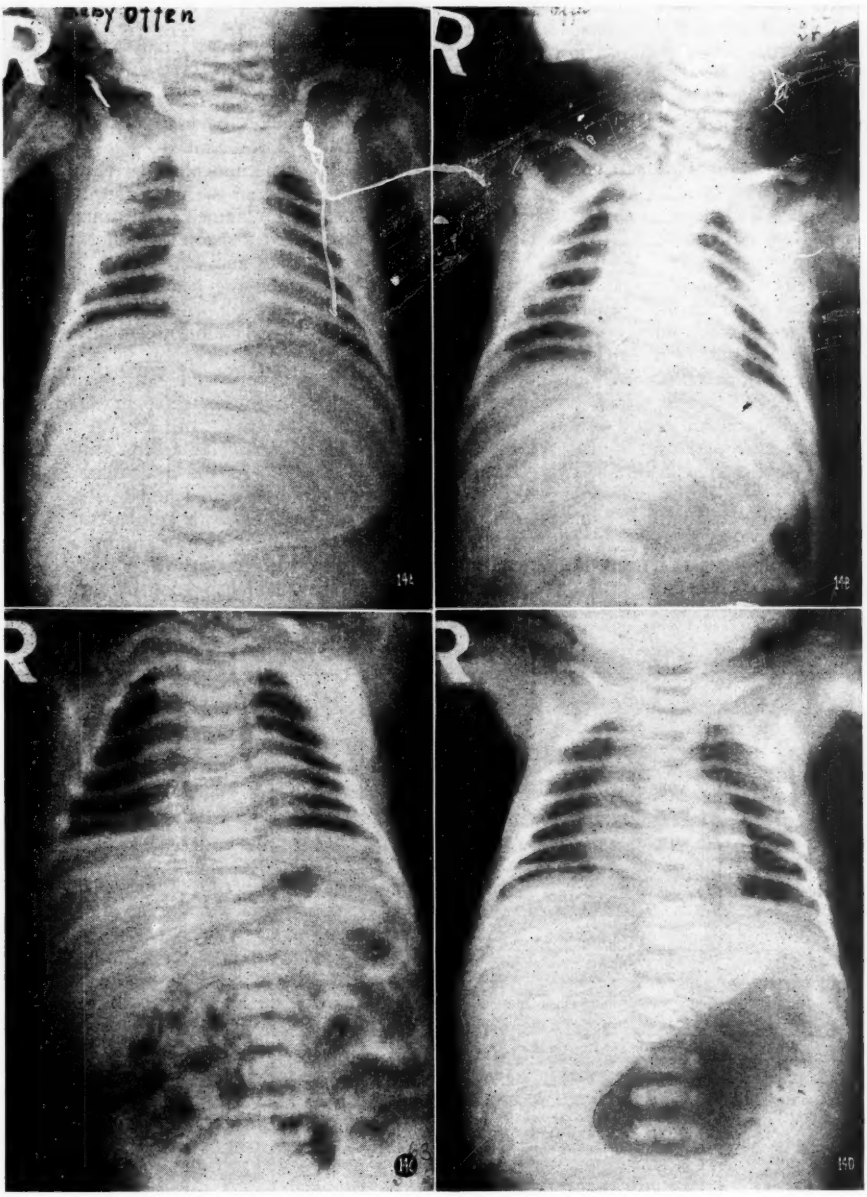


Fig. 14. Case VIII.
Fig. 14*a*. 22 June 1957 (1st day of illness). CTI: 0·65; CD: 5·6 cm. ((*Caffey*).[7]
Fig. 14*b*. 24 June 1957 (3rd day of illness). CTI: 0·59; CD: 5·4 cm.
Fig. 14*c*. 27 June 1957 (6th day of illness). CTI: 0·60; CD: 5·6 cm.
Fig. 14*d*. 3 July 1957 (12th day of illness). CTI: 0·57; CD: 5·8 cm.

disease, and the babies become most ill between the second and third relapses of fever.

All the survivors are known to be alive and well 6 months after their illness, and Cases II and VIII have been examined fully without revealing abnormal physical signs.

CLINICAL FEATURES

The clinical, radiological, electrocardiographic, autopsy and virus studies are summarized in Table I.

In this institution temperatures are taken in the morning and in the evening, so that the onset of fever is known to within 12 hours. Pyrexia was present in all cases and usually followed the path described in Bornholm disease in children and adults. This pattern is not seen in septic infections, and does not resemble the swinging temperatures of abscess formation In severe septicaemia in neonates the temperature may remain normal or hypothermia may occur. One accepts a rectal temperature of up to 99.8° F. as normal.

Tachycardia is always difficult to assess in the newborn, particularly in the crying baby. The normal heart rate is 120–140 per minute and in bouts of crying it may often rise to 180 per minute or more. The rise proportionate to the fever is not therefore readily assessed, and no figures seem to be recorded for comparison with the generally accepted rise of 10 beats per minute for each degree F. rise in temperature in the adult.

Because of the difficulty in feeling the pulse in the newborn, all the heart rates recorded in this series were obtained by auscultation of the apex beat. Extra-systoles are not uncommon in normal babies and were heard here early in Case VIII, when the heart rate was 175 per minute and were confirmed on the ECG (Fig. 13A). In Case IV they were heard on the seventh day on one occasion.

Systolic murmurs were not uncommon and were audible over the whole praecordium and maximal at the apex. In Case VII it appeared as the heart rapidly enlarged, seen radiologically in Fig. 9. As the heart size diminished the murmur disappeared and was never heard again, not even as death approached. In Case VIII a praecordial systolic murmur maximal at the apex was also heard on the second day of the illness and had gone by the third day. X-rays were taken and, unlike Case VII, did

TABLE I: SUMMARY OF FINDINGS

Case No.	*Sex*	*Age at on Onset* (Days)	*Classification*	*Symptoms and Signs in Order of Appearance*	*ECG*	*X-ray**	*Result*	*Histology*	*Isolation of Coxsackie B3 Virus*	*Mother (Symptoms and Virus Studies)*
I KAI	M	8	Severe	Fever. Red throat. Vomiting. Refusal of feeds. Limpness. Dyspnoea. Pallor. Cyanosis. Hepatomegaly.	Not done	0·67	Died	Myocarditis	+ve myocardium	Febrile. Headache. High titre antibodies in blood.
II STE	M	6	Moderate	Fever. Red throat. Cyanosis.	+ve	0·64	Lived		+ve stool	Febrile. Stool negative. No antibodies in blood.
III TRI	F	5	Severe	Fever. Red throat. Moaning. Limpness. Cyanosis. Vomiting.	+ve	Not done	Lived		+ve stool	Coryza. Stool negative. No antibodies in blood.
IV BRI	F	7	Severe	Fever. Red throat. Limpness. Cyanosis. Vomiting. Extrasystoles. Triple rhythm. Systolic murmur. Hepatomegaly. Deep cyanosis.	Not done	Not done	Died	Myocarditis	+ve myocardium	Febrile. Stool negative. No antibodies in blood.
V OLI	M	6	Moderate	Fever. Red throat. Disproportionate tachycardia. Limpness. Cyanosis.	+ve	Not done	Lived		+ve stool	Febrile. Stool negative. No antibodies in blood.
VI NOT	M	6	Severe	Pallor. Dyspnoea. Limpness. Disproportionate tachycardia. Triple rhythm. Cyanosis.	Not done	Not done	Died	Myocarditis	+ve myocardium	Well. Stool negative. No antibodies.
VII HAE	M	6	Severe	Fever. Red throat. Disproportionate tachycardia. Limpness. Hepatomegaly. Systolic murmur. Triple rhythm. Dyspnoea. Cyanosis. Haematemesis. Melaena.	+ve	0·70	Died	Myocarditis	+ve myocardium	Bornholm disease Stool + ve. High titre antibodies in blood.
VIII OFF	M	7	Moderate	Fever. Red throat. Disproportionate tachycardia. Cyanosis. Systolic murmur.	+ve	0·65	Lived		+ve stool	Well. Stool negative. No antibodies in blood.

* Maximum cardio-thoracic index.[7]

not demonstrate any striking increase in heart size (Fig. 14). This murmur reappeared, though much softer, on the seventh day of the disease and was gone again 2 days later. A similar murmur was also heard in the terminal stage of the illness in Case IV. These murmurs are probably due to cardiac dilatation rather than valvular disease, which was not demonstrated at autopsy in any case. It appears that they are of serious import. A pericardial friction rub was not heard, as it was in one adult case with Bornholm disease.[8]

Triple rhythms were heard in severe cases. In Case VII it occurred early on when cardiac dilatation was present, and again in the terminal stages. It was also noted at the end of the disease in Cases IV and VI.

Hepatomegaly was observed in Cases I, IV, VI and VII, all of whom died. In the first 3 cases it appears to have been due to cardiac failure rather than hepatitis, since it occurred when the heart was clearly failing and there was no evidence of hepatitis at autopsy. In Case VII, however, hepatomegaly occurred early and on the basis of past experience was thought to be due to the failing heart. On the fifth day the liver receded as the baby's condition improved, only to enlarge again near the end. At autopsy there was evidence of extensive necrosis, not of very recent origin, and on this basis it may be that the initial enlargement was due to a virus hepatitis, and the terminal stage to congestion. Hepatomegaly must therefore be considered as a sign of grave prognostic import.

Cyanosis was seen at some stage in all the cases. In the moderate cases it usually appeared at the time of the second pyrexial episode, and had a dusky, greyish or ashen tinge, suggestive of peripheral circulatory failure. The more severe the case, the more severe and the earlier was this change, so that in Case VII oxygen was necessary from the beginning of the attack. The deeper grades of cyanosis were observed in the terminal phases and were thought to be due to congestive failure.

Signs of circulatory collapse are common to myocarditis of viral origin and to septicaemia or toxaemia. In septicaemia and toxaemia a toxic myocarditis may provide a common cause. Weakness, failure to suck and changes in skin colour to a dusky grey or ashen tinge are signs common to all these diseases. Depending on the intensity of the infection, they may occur earlier or later in the illness. But in septic and toxaemic states they do not proceed to frank cardiac failure, as occurred here.

The slighter grades of dyspnoea are difficult to assess in the newborn, where the respiratory centre is labile and the respiratory rate erratic. It was often seen in the severe stages of the illness or as congestive failure supervened. Tachypnoea was common, though distress was not usually marked. Case VII had a respiratory rate of 112 per minute from the second to the fourth day, but there was little rib recession, possibly owing to the extremely rapid rate.

Oedema was observed in Case I at the end, but not in the other cases. The salt intake in the other cases was restricted and may have prevented its appearance.

In no case was a bulging fontanelle found or any neck rigidity. Encephalitis was considered in Case I because of the dyspnoea in the absence of chest signs, and a lumbar puncture was done. Since the fluid was crystal clear, no further examination was made, but at autopsy there was histological evidence of meningitis and virus was recovered from the spinal cord.

Case VII developed a terminal left parotitis with swelling of the submandibular salivary glands. At autopsy this was shown to be of septic rather than virus origin.

THE PLACE OF THE ECG IN THE DIAGNOSIS OF COXSACKIE MYOCARDITIS

The ECG findings are summarized in Table II and recorded in the various Figs. referred to in the case histories.

ECG's were recorded in 5 cases, only one of which (Case VII) was fatal. In 3 cases (II, VII and VIII), where graphs were obtained during the acute phase of myocarditis, the changes were limited to depression of the S-T segments and flattening of the T waves. The changes recorded in the first 24 hours of illness in 2 cases were too minimal to permit confident diagnosis (Figs. 10A, 13A), but after the first few days of illness, abnormal changes were present in all 3 cases. This emphasizes the importance of obtaining a series of ECG tracings before excluding the diagnosis on the grounds of an equivocal initial graph. It is likely that the daily ECG would quickly reveal a diagnostic serial change in this type of myocarditis. The changes were never gross, but in the fatal case they became very wide-spread 2 days before death, in keeping with extensive myocardial damage in both ventricles (Fig. 10C). However, in Case VIII, where abnormal changes developed in all chest leads (Fig. 13B) on the fourth day of the illness, the infant's condition remained satisfactory, cardiac failure never developed and recovery was rapid.

TABLE II: ANALYSIS OF ECG FINDINGS

	Case II			Case III		Case V			Case VII			Case VIII		
Day of Illness	6	16	60	12	21	12	21	64	1	2	7	1	5	12
Digitalis	0	+	0	0	0	0	0	0	0	+	+	0	+	+
Rate	165	140	130	130	165	170	160	140	170	140	150	160	120	100
Rhythm	S.T.	S	S	S.A.	S.T.	S.T.	S.T.	S.R.	S.T.	N.T.	S.T.	S.T. V.P.S.	S	S
P-R Interval	0·14	0·14	0·14	0·12	0·12	0·11	0·12	0·12	0·12		0·16	0·12	0·11	0·12
QRS Width	0·05	0·05	0·05	0·05	0·04	0·04	0·04	0·05	0·06	0·08	0·06	0·05	0·06	0·06
QRS Voltage	Low	Low	N	N	N	Low	Low	N	Low	N	N	N	N	N
S-T Segment	Slight depression III, AVF V_{1-3}		N	Slight elevation V_4 and V_6	N	N	N	N	Minimal depression V_3 and V_6	Deformed by P wave	Abnormal in all leads	N	Abnormal V_1 to V_6	N
T wave	Flat V_4–V_6	N	N	N	N	Inversion I, II, V_{4-6}	Inversion I, II, aVL V_6 and V_6	N	N	Deformed by P wave	Flattening in all leads	Inversion III and aVF	Abnormal V_{1-6}	N
QT_c	0·38	0·36	0·41	0·32	0·33	0·33	0·39	0·34	0·41	0·36	0·42	0·35	0·36	0·34
Diagnosis	+	N	N	?+	N	+	+	N	?+	Abnormal rhythm	+	?+	+	N

Abbreviations: S.T. — Sinus tachycardia; N.T. — Nodal tachycardia; S — Sinus rhythm; V.P.S. — Ventricular premature systoles; S.A. — Sinus arrhythmia

This illustrates the limitations of electrocardiography in conveying information about the functional status of the myocardium and prognosis.

Abnormal changes occurred in every case, although in Case III the graph taken on the twelfth day of illness revealed only trivial changes suggestive of epicardial damage (Fig. 5A). It is probable that had an ECG been taken earlier, more impressive abnormalities would have been noted. In all cases which survived, the ECG returned to complete normality. A normal graph was recorded on the 12th, 14th, 21st and 64th days after the onset of the illness in Cases VIII, II, III and V respectively. Had graphs been recorded more frequently, return to normality might well have been detected earlier. Also, more information might have been obtained about the changes indicating healing. It is felt that the symmetrical inversion of the T waves recorded in Case V on the 12th and 21st days (Fig. 8) of illness may reflect the process of healing as this infant had been apyrexial and asymptomatic for five days prior to the first ECG.

Since the diagnosis depends on S-T segment and T wave changes during the acute phase of myocarditis, it will be appreciated that difficulty in interpretation may arise once digitalis has been administered. Knowledge of the quantity of digitalis already given and measurement of the QTc gave helpful information. For example, in Case VII the possibility of digitalis effect had to be seriously considered in the graph taken on the seventh day of the illness because nodal tachycardia had developed (Fig. 10B) during the first 24 hours of digitalis therapy. However, it was considered that the extensive changes were much more like those of myocarditis because the dosage of digitalis had never been excessive and the QTc had become prolonged to the outermost limit of normal. This opinion was confirmed by the finding of severe myocarditis at necropsy 2 days later. Digitalis in toxic doses usually results in shortening of QTc, whereas QTc either remains normal or becomes prolonged in myocarditis. Electrolyte imbalance may arise from excessive vomiting, diarrhoea or sweating associated with inadequate replacement therapy. This may also induce S-T segment and T wave changes indistinguishable from those shown in Fig 10C and Fig. 13B.

All cases had sinus tachycardia. One case developed nodal tachycardia (Fig. 10B), which might have been induced by digitalis, and one case showed ventricular premature beats (Fig. 13A). The P-R interval was normal in every case, except pre-terminally in Case VII, when it became slightly prolonged (0.16 second). The QRS voltage often appeared to be low initially, but always improved later. The QRS time remained within normal limits in all cases. The QTc remained within the range of normal varying from 0.34 to 0.42 second in the 14 ECG's done on 5 cases.

Although the series is very small and the opportunity for more detailed and frequent studies was limited, the following conclusions can be drawn. All 5 cases revealed abnormal ECG changes, provided the precaution of recording serial ECG was taken when the initial graph was inconclusive. The changes associated with the early phase of myocarditis were limited to shifts of the S-T segments and minor changes in the T wave. These occurred predominantly over the left ventricle but were very extensive pre-terminally in the fatal case. Abnormal Q waves or disappearance of R waves were not observed, but might be anticipated in cases with more severe myocardial damage. Symmetrical inversion of the T waves unassociated with shift of the S-T segment probably indicates healing during the recovery phase. The graphs returned to complete normality in all the surviving cases.

X-RAYS

All X-rays were taken supine with a portable machine at a distance of 33 inches, while the baby was in the cot. This will slightly affect the normal figures for the diameter of the heart (CD), but will not affect the cardiothoracic index (CTI) as measured by Bakwin and Bakwin.[9]

X-rays were taken in Case I on the fourth and fifth (the last) days of the illness. In neither did the heart appear abnormal, although the CTI increased from 0.62 to 0.67. The heart was enlarged at autopsy.

In Case II an X-ray was taken on the fifteenth day of the illness during a relapse and the CTI was 0.64.

In Case VII (Fig. 9) X-rays were taken on the second, fourth, sixth and ninth days of the illness, the last occasion being the day before death. The CTI's were 0.61, 0.70, 0.61 and 0.57 respectively. The appearance of a systolic murmur coincided with the increase of the CTI on the fourth day, and had disappeared by the sixth day, when the CTI had returned to normal.

In Case VIII (Fig. 14) X-rays were taken on the first, third, sixth and twelfth days of the illness. The CTI's were 0.65, 0.59, 0.60 and

0.57 respectively. A systolic cardiac murmur was heard on the second and third days, and again on days 7–10, after which it was not heard again. In this case the first appearance of a systolic murmur was not accompanied by cardiomegaly, but no X-rays were taken when the murmur re-appeared. It is possible, after considering Case VIII in which the radiological cardiomegaly was so transient, that it was present in this case.

Bakwin and Bakwin[9] give the CTI in the newborn as 55.31 with a standard deviation of 4.94, so that a CTI of 45–65 may be accepted as within normal limits. The reasons for this wide variation are the difficulties of ensuring the precise phase of respiration, and the exposure. In only 2 plates of this series, therefore (the second X-rays of Cases I and VII) may the X-rays be regarded as definitely indicating cardiomegaly. The exhibition of serial changes in size at about the same stages of respiration is more valuable than a single estimation.

From these observations it appears that radiography has little to offer in the diagnosis and prognosis.

TREATMENT

As soon as the autopsy in Case I confirmed the diagnosis, Cases II—V were placed on a full cardiac failure regime, although they were not at that stage in cardiac failure. The same procedure was adopted for Cases VII and VIII, with certain variations.

Bed Rest. The babies were nursed flat at all times because of the risk of cardiac arrest if lifted from the supine position. They were tube-fed and given Chloral Hydrate gr. 1 as often as necessary to ensure absolute quiet.

Fluid Intake. Cases II, IV and V were fed 20 oz. (568 ml.) per day, and Case III, 17½ oz. (497 ml.) per day in 5 divided feeds. Cases VII and VIII were fed 12 oz. (341 ml.) daily in 4 divided feeds 6-hourly. It is interesting to note that in these 2 cases the weight loss was very small in spite of the low fluid and caloric intakes (120 calories a day).

Salt Intake. The sodium content of human milk is about 0.015% and that of cow's milk about 0.058%.[10] Owing to the emptying of the nursing home, it proved impossible to obtain sufficient breast milk for all cases in the first outbreak, though sufficient was available for the second. In the first outbreak the sodium intake was of the order 0.2 g. sodium chloride daily; and in the second, when the breast milk was freely obtained, it was about 0.06 g. daily. No oedema was seen except in Case I, which was untreated.

Digitalis. All cases received Digitalis Folium in a dose of ¼ gr. 8-hourly, given for 3 days, and thereafter ½ gr. daily for maintenance. This is approximately equivalent to 2½ gr. per 10 lb. body weight given in divided doses over 3 days, with a maintenance dose of 1/10th of the total. Digoxin was not used, but may well be preferable if the baby is in cardiac failure when first seen, since its action is more readily achieved and the drug is more rapidly excreted. It should be given in the comparable dose of 0.04 mg. per lb. body weight given over 3 days in divided doses, with a maintenance dose of 1/10th of the total.

It is difficult to distinguish the effects of digitalis intoxication from those of myocarditis, both clinically and electrocardiographically. Coupling of the heart beats occurred in Case II and led to the digitalis being stopped. Vomiting occurred occasionally, and was thought to be a digitalis effect in Case IV, who died late in the illness. In retrospect this was more probably due to gastric congestion.

In no case was an attempt made to lower the heart rate below 120 per minute with digitalis by pressing the dose. Though bradycardia is clearly desirable as a measure to rest the heart, one is reluctant to risk ventricular arrest, where the myocardium is already known to be diffusely and seriously damaged.

Mersalyl. Mersalyl was given in a dose of 0.5 ml. to Cases I and IV in the terminal phase without apparent benefit.

Oxygen. Oxygen was given in a concentration of about 40% in the tent. In Case I a dramatic change was observed and the baby changed from deep cyanosis to a bright pink in a matter of minutes. In general it improved the colour of the distressed babies and was sufficient to bring relief from restlessness.

Antibiotics. Chloromycetin, Polycycline and Ilotycin were used. Chloromycetin was given in a dose of the order of 40 mg. per lb. body weight per day, and the other two 12 mg. per lb. body weight per day. No influence on the temperature was observed. However, Case VII exhibited a terminal parotitis which, at the time, was thought to be of virus origin, but at autopsy it was disclosed that the cause was septic. It might have been of value to use antibiotics prophylactically in the later stages against such an event.

Ascorbic Acid. Ascorbic acid was not given to Cases II–V, because newborn babies are born with an adequate reserve. Nevertheless

Cases VII and VIII received a supplement of 25 mg. daily in case it should help in the reparative process.

Gamma Globulin. Gamma globulin was not given to any case. Its content of Coxsackie virus antibodies is not known to us and its effect, once the virus is in the myocardium, is problematical.

In general the treatment suggested here, together with the excellent nursing care available, sufficed to bring Cases II–V and VII–VIII through the early phase, Case VII being especially severe. It was insufficient to prevent the deaths of Cases IV and VII during the phase when recovery could be expected.

As it is a cardinal principle of the treatment of inflammation to rest the affected part, and this is so difficult where an organ's function cannot be arrested, some other method must be sought to achieve bradycardia in order to bring the severely ill cases through their reparative stage.

Hypothermia immediately comes to mind, but such evidence as there is contra-indicates its use. Boring *et al.*[11] found that if adult mice, infected with the Conn. 5 strain of Coxsackie virus, were chilled to 4° C. (39° F.) then dissemination of the virus occurred with fatal results. Usually this virus is confined to the pancreas. Admittedly cold of this order is far greater than would be practised in Man, but further experiments would be necessary to determine the critical level, and even then would not be directly applicable to Man.

The use of cortisone is also problematical. Again in adult mice a single injection of 2.5 mg. of cortisone converts the local reaction to Conn. 5 strain of the Coxsackie virus to a systemic disease with fatal consequences.[12, 13] Cortisone is known to aggravate the disease processes of other virus infections and would not seem to be advisable.

Until such time as specific antiviral therapy becomes available, it is difficult to see what other measures can be taken to lighten the load on the distressed heart.

DISCUSSION

It may be expected that outbreaks such as those described here will occur in increasing numbers, unless complete segregation of mothers with their children becomes a routine in maternity institutions, and unless visitors are excluded and barrier nursing imposed. The incidence, however, may be modified by the possession by the newborn of a passive immunity obtained from its mother. The question of immunization of females of child-bearing age has to be considered.

In the absence of specific antibiotics or other virus antagonists, early diagnosis and the imposition of full cardiac failure treatment is the only method open to us. That it may achieve something is shown by the fact that Cases I and VI died almost untreated very early in their illness in the acute phase, whereas Cases IV and VII, who were actively treated early on, survived until the repair stage of their disease.

It is apparent from this and past outbreaks, that Coxsackie myocarditis is a severe condition with a high mortality, but provided life can be sustained, there is no reason to suppose that complete recovery may not occur with full expectation of the life span. This enjoins a conservative approach, with the accent on cardiac rest. The difficulty is to rest the heart, particularly in view of the physiological tachycardia of the newborn infant.

The early diagnosis of Coxsackie myocarditis is most difficult. It depends on the awareness that a pyrexial illness in the neonatal period may be due to the virus. The presence of an epidemic of Bornholm disease in the community at large, or a case in the nursing home, may alert the practitioner further. The history of maternal and family illness was valuable in Case VII, and it was because of this that it was thought justifiable to institute treatment for myocarditis without delay, in the absence of clinical or definite ECG evidence.

In the early stages of the illness, the only constant abnormal findings were a red throat and pyrexia. The former sign was usually well marked and is not a feature of septic infections at this time of life. It is from septicaemia that the virus diseases require differentiation; nevertheless it was not deemed advisable to withhold antibiotics, however certain the diagnosis.

Signs common to viraemia and septicaemia include pyrexia, tachycardia, loss of activity and ability to suck, signs of circulatory collapse, and perhaps diarrhoea and vomiting. Jaundice is a feature of neonatal sepsis and often occurs early, but it was not seen in this series despite the histological evidence of hepatitis in Case VII. The presence of pyodermia or umbilical sepsis may indicate a portal of entry and suggest septicaemia. Dyspnoea is common to both cardiac failure and staphylococcal pneumonia, but clinical and X-ray examination should suffice to distinguish the conditions, though Case I was considered to be pneumonic in the early stages, until the ap-

pearance of frank cardiac failure clarified the diagnosis.

In later cases, the occurrence of fever and tachycardia was sufficient indication for ECG and X-ray examination, not only to establish the diagnosis but also to obtain information for later comparison. The ECG was taken on the first days of the illness in Cases VII and VIII. In both, trivial changes were present, but at the time they were too doubtful for a positive diagnosis of myocarditis. This failure of the ECG to reveal pathological changes at the onset of myocardial disease, be it inflammatory, ischaemic, allergic, etc. is a well-known pitfall and always demands the use of serial ECG's, which did, in fact, establish the presence of myocarditis in these as well as all the other cases.

It is clear that Coxsackie virus infection is not always associated with myocarditis in the newborn, but it must be stressed that its presence may easily be missed in the case of sudden death or in the absence of specific investigations. This might well have occurred in this series but for the firm establishment of the diagnosis by necropsy in Case I. It appears that the severity and extent of the disease in the human neonate is comparable with that in the suckling mouse, and that the adult form is more benign, as it is in the mouse.

SUMMARY

1. Eight cases of proven Coxsackie B3 virus myocarditis in the newborn are described with a mortality of 50%.

2. The age at onset varied from 5–8 days.

3. The importance of taking the temperature of newborn infants is stressed. This, in addition to the presence of an epidemic or suggestive symptoms in the mother, is a valuable guide to the onset of the disease.

4. Pyrexia and inflammation of the throat are the most constant initial findings, and are alone sufficient to alert the practitioner.

5. Tachycardia is most difficult to assess, but a rate of over 160 per minute in a quiet baby is suggestive. In several cases the heart rate was normal.

6. Signs of cardiac failure may first draw attention to the severity of the disease.

7. Diarrhoea and jaundice were not features of this series, though one case referred to in the virological studies was said to have loose stools.

8. Serial, possibly daily, ECG's may be necessary to reveal abnormality and establish the diagnosis. ECG's are not of prognostic value in the acute phase.

9. X-rays are of little diagnostic or prognostic value.

10. The differential diagnosis between myocarditis and neonatal sepsis may be difficult and is discussed. Antibiotics should not be withheld in case there is a diagnostic error, and is of value in the prevention of secondary infection.

11. The treatment is that of cardiac failure from the time that the disease is suspected. Avoidance of stress, flat nursing, tube feeding, restriction of salt and fluids, sedatives, digitalis and oxygen all play a part.

12. Gamma globulin was not used, but might be worth a trial. Cortisone and hypothermia are contra-indicated without further research.

13. It is not sufficient to cease treatment at the end of the febrile period.

14. The following questions are reported and discussed elsewhere in this issue:

(*a*) Virus studies of the babies and mothers.

(*b*) Epidemiology and prevention of spread.

(*c*) The malignance of the disease in the newborn.

(*d*) Histological studies.

We wish to acknowledge the assistance of the Department of Pathology of the University of Cape Town, particularly in the first case, where the report of the frozen section by Dr. C. J. Uys and Dr. M. L. Simenhoff put the diagnosis on a firm basis.

Dr. I. P. Jaffe kindly gave us a report on Case VI, and on the relapse in Case II.

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OPSOMMING

1. Ag gevalle van bewese Coxsackie B3-virus-hartspierontsteking by pasgeborenes, met 'n sterftesyfer van 50%, word beskryf.

2. Die ouderdom by die aanvang van die siekte het gewissel van 5 tot 8 dae.

3. Die belangrikheid van die aantekening van die temperatuur van pasgebore kinders word beklemtoon. Dit, asook die aanwesigheid van 'n epidemie of suggestiewe simptome by die moeder, is 'n waardevolle aanduiding vir sover dit die aanvang van die siekte betref.

4. Pireksie en ontsteking van die keel is die mees konstante aanvanklike bevindings, en is voldoende om die geneesheer op sy hoede te stel.

5. Hartversnelling is besonder moeilik om te bereken, maar 'n snelheid van meer as 160 slae per

minuut by 'n stil babetjie is suggestief. In etlike gevalle was die hartslag normaal.

6. Tekens van hartversaking kan aanvanklik die aandag op die erns van die siekte vestig.

7. Diarree en geelsug was nie kenmerke in hierdie reeks nie, hoewel daar verklaar is dat los ontlasting voorgekom het by een geval waarna in die virologiese studie verwys word.

8. Periodieke, moontlik selfs daaglikse elektrokardiogramme kan nodig wees om abnormaliteite aan die lig te bring en diagnose te bevestig. Tydens die akute fase het elektrokardiogramme geen prognostiese waarde nie.

9. X-strale is van min diagnostiese of prognostiese waarde.

10. Die differensiële diagnose tussen hartspierontsteking en neogeboortelike sepse kan moeilik wees, en word bespreek. Antibiotica moet nie weerhou word nie in geval daar 'n diagnostiese vergissing is, en is van waarde vir die voorkoming van sekondêre infeksie.

11. Die behandeling is dieselfde as in die geval van hartversaking vanaf die oomblik dat die siekte vermoed word. Die vermyding van spanning, verpleging in 'n plat posisie, buisvoeding, beperking van sout en vloeistowwe, kalmeermiddels, vingerhoedskruid en suurstof speel almal 'n rol.

12. Gamma-globulien is nie gebruik nie, maar dis miskien die moeite werd om dit op die proef te stel.

13. Dit is nie voldoende om die behandeling te staak na afloop van die koorsige tydperk nie.

14. Die volgende aspekte word elders in hierdie uitgawe gerapporteer en bespreek:

(*a*) Virus-studies van die babetjies en moeders.

(*b*) Epidemiologie en voorkoming van die verspreiding van die siekte.

(*c*) Die kwaadaardigheid van die siekte by pasgeborenes.

(*d*) Histologiese studies.

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COXSACKIE VIRUS MYOCARDITIS OF THE NEWBORN

A PATHOLOGICAL SURVEY OF 4 CASES

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As there are few reports in the literature on the pathological findings in Coxsackie virus myocarditis in Man[1—4] it is thought worth reporting the following 4 cases in detail. In addition, as the cases are of varying duration, we believe that some contribution to the pathogenesis of the cardiac lesion can be made. The presence in all but one of hitherto undescribed liver lesions, is regarded as significant.

In each case multiple sections were taken from all chambers of the heart (including the apex), the interventricular septum and the papillary muscles of the left ventricle. These were fixed in 10% formol-saline and stained with haematoxylin and eosin and, where indicated, the special stains done were Mallory's phosphotungstic acid haematoxylin, von Gieson's, Prussian blue, methylene blue and eosin, toluidin and von Kossa. Frozen sections of the myocardium were stained with Scarlet Red for fat.

The cases described below are enumerated as in the accompanying articles in this issue.

AUTOPSY FINDINGS

Case VI. The autopsy was performed 30 hours after death. The body was that of a well-covered, European, male infant, 8 days old, weighing 3,526 g. and 52 cm. long. There

was no evidence of jaundice, cyanosis or oedema. The pericardial cavity contained about 5 ml. of clear yellow fluid but showed no sign of exudate. The other serous cavities were normal.

In the heart (22 g.) the only changes of note were slight left ventricular dilatation associated with a glistening and pale myocardium. The endocardium, valves, coronary vessels and aorta were not remarkable. The lungs (right 49 g., left 52 g.) were diffusely congested and at the left apex the substance was firm but not friable. The liver (157 g.) was a firm glistening organ; its cut surface showed congestion and the mottling of focal fatty change. The kidneys (39 g.) and brain (430 g.) were congested. The remaining viscera were normal.

Microscopically protein-rich interstitial fluid was present in all the sections of myocardium. In addition, however, this case (Figs. 1 and 2) was characterized by:

(*a*) A variable pattern of involvement in which some sections showed extensive confluent necrosis and others no more than oedema; and

(*b*) A relatively minimal inflammatory response to some foci of necrosis.

The cytoplasm of the affected necrotic fibres stained poorly and in some areas only the outline of the cell remained. Concurrently the nuclei showed changes varying from pyknosis to karyolysis with chromatin debris scattered amongst the inflammatory cells. Polymorphonuclears predominated and were focally distributed in the areas of necrosis and adjoining interstitial tissues, but some of the areas of recent necrosis were virtually free of them. Many of the polymorphonuclears assumed the angular and elongated form of migrating cells. Amongst the polymorphonuclears were a small proportion of histiocytes, some showing the nuclear detail of Anitschow myocytes. Related to the foci of necrosis were dilated and congested capillaries. The subpericardial connective tissue was markedly oedematous and contained an infiltrate of polymorphs, but a surface exudate was not apparent.

The pleura and pulmonary septa were oedematous. In the lungs were foci of intra-alveolar haemorrhage and collapse and some alveoli contained haemosiderin-laden macrophages. The brain showed no changes of note, but the meninges contained numerous macrophages and their capillaries were engorged and dilated. Sections of kidneys (congested), small and large gut, liver, stomach, adrenals (evidence of involution of the cortex), thymus, thyroid, tongue, pancreas, lymph nodes, spleen, prostate, aorta and pulmonary artery revealed no abnormal findings.

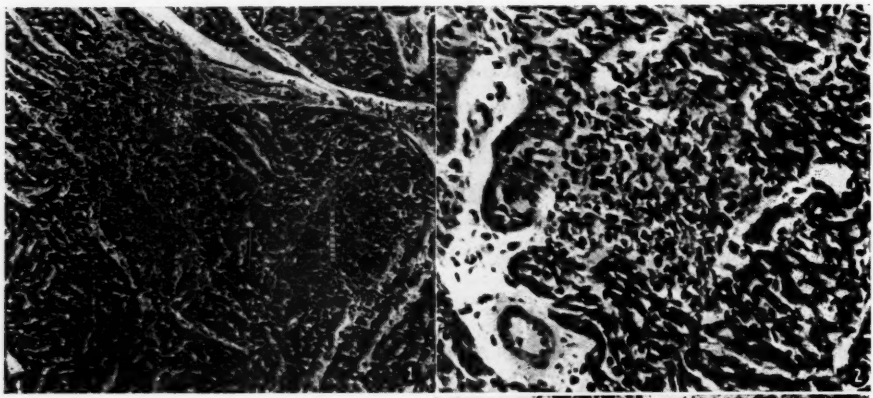


Fig. 1. Case VI: Duration of illness 2 days. Under a low magnification this illustrates the focal nature of the acute cardiac lesions. The inflammatory exudate is most intense in the foci of muscle fibre destruction but can be seen in the interstitial tissues as well. (H & E × 134).

Fig. 2. Case VI: Duration of illness, 2 days. A higher magnification illustrates the complete destruction of the muscle fibres and the nature of the accompanying inflammatory infiltrate as seen in the acute lesions. (H & E × 223).

Fig. 3. Case I: Duration of illness, 5 days. Capsule of liver showing thick, rather acellular. fibrinous exudate. Except for signs of extramedullary haemopoiesis, the underlying liver tissue is normal. (H & E × 160).

Case I. The autopsy was performed 17 hours after death. The subject, a European male infant, 14 days old, weighed 3,440 g. and was 52 cm. long. The face was puffy but there was no obvious peripheral oedema. The jugular veins were distended with blood. The pericardial sac contained approximately 5 ml. of clear yellow fluid and the peritoneal cavity 20 ml. of similar fluid. The heart (25 g.) was a dilated pale organ which showed scattered subepicardial purpuric haemorrhages, but no pericardial exudate. The endocardium and valves were normal but the myocardium was pale, translucent and shining. The foramen ovale and ductus arteriosus were patent, and the aorta was normal. The liver (172 g.) was enlarged, tense and glistening and the gall bladder was almost completed embedded in its substance. The capsule of the inferior surface of the left lobe showed a thin fibrinous exudate, and on section the liver substance appeared oedematous and mottled.

The lungs (right 50 g., left 40 g.), kidneys (36 g.), brain (444 g.) and other organs were not remarkable.

Striking histological changes were present in the myocardium. These consisted of pronounced diffuse intracellular and intercellular oedema and extensive focal necrosis with cellular infiltration, confluent in places. The muscle fibres in the necrotic areas stained poorly and occasionally disappeared almost completely, leaving only scattered masses of chromatin. The associated polymorphonuclears were frequently elongated and angular, as in migrating forms. There were also moderate numbers of plump, fusiform cells with open vesicular nuclei of histiocytic type. Similar cells showing the central nuclear chromatin bar of Antischow myocytes occurred quite frequently. In addition, but in far fewer numbers, were lymphocytes, plasma cells and eosinophils. The inflammatory exudate was most pronounced in the areas of muscle necrosis but occurred elsewhere in the interstitial tissues as well. In the areas of necrosis and inflammation the capillaries were unduly prominent and congested and activation of their lining endothelial cells was apparent.

Although the majority of sections showed these changes—most marked in those from the left ventricle—there were isolated sections which showed minimal or no involvement at all.

In all the sections from the inferior surface of the left lobe of the liver, the presence of a fibrinous exudate was confirmed (Fig. 3). Surprisingly enough, no morphological changes were evident in the underlying liver tissue. Elsewhere the liver cells showed slight focal fatty change, some of the Kupffer cells contained occasional small granules of haemosiderin; the portal tract showed the normal infiltration of lymphocytes and there were frequent foci of extramedullary haemopoeisis.

The alveolar walls of the lungs were slightly thickened by congestion and histiocytic infiltration, and small areas of intra-alveolar haemorrhage with macrophage infiltration were present. In spite of notable oedema of the pleura and septa, there was no fibrinous pleurisy.

The adrenals were of the foetal type and showed no evidence of involution. Except for oedema, which was a feature of most tissues, sections of the pancreas, thyroid, tongue, brain, prostate, spleen, aorta, intestine, kidney, thymus, trachea and bone marrow showed no special histological features.

Case VII. The autopsy was performed 14 hours after death. The subject, a European male infant of 16 days, was well nourished, weighed 3,304 g. and was 54 cm. long. There was no evidence of oedema, cyanosis or jaundice. Swelling of the left parotid region and of the right scrotum was present, the latter containing fluid that could be emptied into the peritoneal cavity.

The jugular veins were engorged. The pericardial cavity contained about 50 ml. of clear yellow fluid but no exudate. The heart (31 g.) showed slight right ventricular dilatation. The myocardium was pale and glistening and over the posterior wall of the left ventricle it had a mottled appearance. Over the papillary muscles there was extensive subendocardial haemorrhage which extended well into the myocardium. The valves were normal, the foramen ovale was patent and the ductus arteriosus had closed. The coronary vessels and aorta were normal. The lungs (right 45 g., left 47 g.) were well expanded except for occasional small areas of alternating emphysema and collapse. The right subapical zone was slightly firmer than the rest. No exudate was present on the pleural surfaces. The tongue showed 2 small haemorrhages at its tip. The peritoneal cavity contained approximately 200 ml. of clear fluid. There was a small haemorrhage into the stomach wall and the rest of the gastro-intestinal tract was normal.

The liver (135 g.) showed striking changes. Over the anterior surface of the right lobe there was a fine fibrinous exudate, but it was absent elsewhere. The lobular pattern of the cut surface of both lobes was obscured by an extensive mottling of alternating haemorrhagic and pale areas, up to 3 mm. in diameter. There was evidence of only slight oedema.

The kidneys (59 g.) were large and oedematous and on the cut surface the glomeruli stood out as prominent red dots. The bladder showed one small haemorrhage at the base. The body of the right testis was completely haemorrhagic and was associated with a communicating hydrocoele, but the epididymis was unaffected. The left parotid was enlarged and congested. The skeletal muscle appeared very pale and somewhat oedematous. The brain (467 g.) was soft and translucent and the rest of the organs were normal.

An arresting histological feature of the myocardium of this case was the presence of lesions of

different ages. Mainly in the wall of the left heart, but to a lesser extent in the right, were changes which appeared to be of some duration. In contrast, a single acute lesion of obviously shorter duration was present in the mitral papillary muscles. In the left ventricle there was confluent necrosis in which the muscle fibres had mainly disappeared and those that remained showed all stages of disintegration. Relatively few inflammatory cells were present, mainly polymorphonuclears and histiocytes, but in addition there were moderate numbers of fibroblasts. The only recognizable nuclei in these areas were those of inflammatory cells. The wall of the left auricle also showed extensive necrosis extending to the endocardium, where the remnants of necrotic fibres existed as thin wisps, some of which had undergone calcification. Acute inflammatory changes were strikingly absent, but lymphocytes and histiocytes were present in moderate numbers and here also was evidence of fibroblastic proliferation. The overlying endocardium was thickened and oedematous and contained prominent elastic fibres. The acute lesion in the tip of the papillary muscle consisted of pronounced recent haemorrhage associated with extensive necrosis of the myocardial fibres. Inflammatory signs were virtually absent.

The liver (Fig. 4) showed extensive focal necrosis which was periportal in many lobules but had no constant zonal distribution; in the more extensive areas the lobular pattern had disappeared, due to confluence of the lesions and collapse of the reticular framework. In such areas many liver cells had disappeared. Those that remained were either necrotic and consisted of eosinophilic remnants with faint nuclear staining or appeared degenerate. There was an associated accumulation of histiocytes, occasional haemosiderin-laden macrophages and lymphocytes. Some foci showed acute haemorrhage and others fibroblastic proliferation with early collagen formation. Around the necrotic foci the liver cells occurred in syncytial masses with a striking alveolar arrangement resembling bile ducts. No true multinucleate giant cells were present and although there were occasional mitoses in the liver cells, no significant degree of regeneration of the liver cells or of the bile ducts was present. Elsewhere there was some oedema and the sinusoids were dilated and congested. Extensive extra-medullary haemopoeisis was present. A well-marked capsular exudate without cellular reaction or evidence of organization was a notable feature.

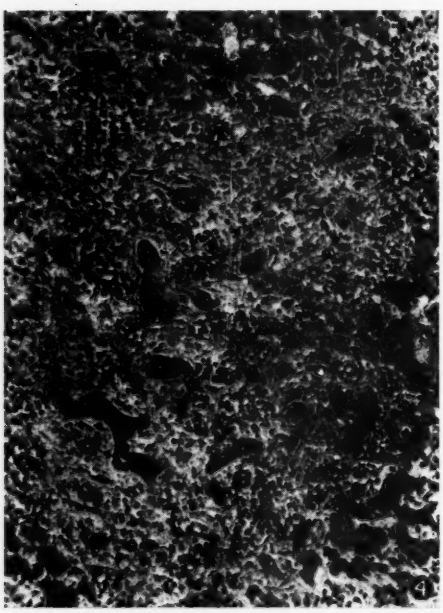


Fig. 4. Case VII: Duration of illness, 9 days. Liver showing areas of focal necrosis with no set zonal distribution. The affected liver cells have largely disappeared and those that remain show signs of regeneration. There is fibroblastic activity, new formation of collagen, and an associated chronic inflammatory response. (H & E × 160).

A striking feature of the spleen was extensive exudation of fibrin into the pulp. This occurred between the sinusoids and the follicles as lakes of eosinophilic, faintly fibrillar material and was unassociated with a significant cellular inflammatory reaction. In between such areas the histiocytic cells were prominent though not present in increased numbers and there was evidence of recent haemorrhage. The spleen, like the liver, showed marked extra-medullary haemopoeisis.

The kidneys showed diffuse oedema. The cortex contained occasional groups of glomeruli showing focal necrosis. The tufts of these were partially replaced by hyaline fibrinoid material in which all detail was lost. In the intact portion of the tuft there were proliferative changes. The tubules from these tufts were necrotic and the neighbouring interstitium contained groups of mononuclear cells. One minute vessel contained a mural thrombus, but its further identification was impossible.

The left parotid showed an acute suppurative parotitis with sub-total necrosis. These areas were teeming with bacilli.

Multiple sections were taken from the brain including the basal ganglia, pons, medulla, cerebellum and cerebrum and in some of these groups of macrophages were present in the meninges. The only other change worthy of comment was a slight increase of microglia in the pons. There was no evidence of perivascular cuffing.

The right testis showed diffuse recent haemorrhage without cellular reaction. The lungs contained increased numbers of haemosiderin-laden macrophages. The pancreas was diffusely oedematous with occasional foci of perivascular histiocytic infiltration. Other tissues examined were skeletal muscle, interscapular fat pad, aorta, prostate, tongue, gut, thymus and thyroid. These were normal histologically.

Case IV. The autopsy was performed 12 hours after death. The subject, a large European female infant, 18 days old, weighed 3,626 g. and was 55 cm. long. There was no jaundice but a mild degree of subcutaneous oedema was present.

There were about 10 ml. of clear yellow fluid in the pericardial sac. The heart (30 g.) appeared much enlarged, largely due to left ventricular dilatation. On section, the left ven-

tricular myocardium was mottled and haemorrhagic. The endocardium was pale, the valves were normal and the foramen ovale was closed. The coronary vessels were normal, as was the aorta.

The lungs (right 51 g., left 40 g.) were firm, especially the left lower lobe and, on section, mottled. The right pleural space contained about 10 ml. of clear straw-coloured fluid but both pleural surfaces were normal. The liver (169 g.) was tense and the cut surface appeared oedematous and mottled. The pancreas, stomach and intestines, kidneys (36.5 g.) and brain (476 g.) were normal, and the remaining organs showed no special features.

Histologically the myocardial lesions were dominated by features of chronicity and repair (Fig. 5). Interstitial oedema, while present, was not pronounced, nor was necrosis. In the affected areas dissolution of the necrotic myocardial fibres was complete, these being replaced by proliferating fibroblasts and an inflammatory infiltrate of polymorphonuclears, lymphocytes, plasma cells and histiocytes in roughly equal proportions. With this fibroblastic proliferation there was also collagen formation, and many capillary-type blood vessels and occasional eosinophils were noted. These features gave these foci a more than superficial resemblance to organizing ischaemic lesions so commonly seen in the adult.



Fig. 5. Case IV: Duration of illness, 11 days. No muscle fibres remain in the affected foci, these being replaced by scar tissue consisting of mature fibroblasts, collagen, frequent thin-walled capillaries and varying numbers of chronic inflammatory cells. (H & E × 160).

The lungs showed a minor degree of collapse, septal oedema and haemorrahge, and a fibrinous exudate on one aspect of the pleural surface. Large numbers of macrophages were present in the pulmonary alveoli. The liver cells, which were separated by oedema fluid, showed glycogen vacuolation of the nuclei and mild fatty change; some iron pigment was present in the Kupffer cells. Sections from the inferior surface revealed a fibrinous exudate infiltrated by polymorphonuclears, but with no organization or evidence of underlying liver involvement. In the brain the only changes worthy of comment were 2 foci of perivascular lymphocytic infiltration in the cerebellum. The remaining sections of striated muscle, spleen, tongue, pancreas, thyroid, intestine, stomach, bladder, kidney and ovary were normal.

BACTERIOLOGICAL FINDINGS

Bacteriological studies on the blood and organs of these 4 cases revealed only those organisms frequently encountered in autopsy material, and to which no significance could reasonably be attached in the present studies.

SUMMARY OF HISTOLOGICAL FINDINGS

Cases VI, I, VII and IV died 2, 5, 9 and 11 days respectively after the onset of the illness. To trace the evolution of the lesion the cases are presented in this chronological order.

Histologically, the cardinal feature of the myocardium was patchy necrosis which generally involved the entire heart, but varied in extent and intensity at different sites. This was most severe in the left ventricle, where foci tended to become confluent. Two days after the onset of the illness, the necrotic muscle fibres were clearly visible but stained poorly and in some only the outlines remained. Already at this stage significant nuclear changes were noted, mainly consisting of pyknosis and karyorrhexis, but also including karyolysis with release and distribution of the chromatin debris. After 6 days there was evidence that the process of cellular autolysis had advanced. While some recognizable necrotic fibres still persisted, many had disintegrated completely leaving only scattered masses of chromatin. Lesions seen on the 9th day, in addition showed calcification of dead fibres. By the 11th day cellular dissolution was complete, few recognizable fibres remained, and the necrotic areas were more clearly demarcated from the

surrounding healthy muscle. At this stage the inflammatory reaction was the only indication of what had occurred.

Polymorphonuclear leucocytes were the principal inflammatory cells. They appeared in the earliest lesions, although necrosis existed without them; after 6 days they were present in maximal numbers, many in the elongated form of migrating cells. Even in the earliest lesions (2 days) some histiocytes of Anitschow myocyte type were seen.

Polymorphonuclears persisted, but in the later stages diminished in number; lymphocytes, plasma cells and histiocytes, however, increased to roughly equal proportions. Eosinophils appeared late and remained relatively scanty. Fibroblasts were evident on the 9th day, but by the 11th day they dominated the picture, and the speed of the repair processes was striking even in an infant where such processes are normally rapid. This was mirrored by the demonstration of well-formed collagenous fibres in these lesions. It was not surprising that, with all this activity, capillary dilatation was a prominent feature and in the later stages many of the capillaries were of granulation tissue type and clearly of new formation. Although many of the inflammatory foci extended to pericardium and endocardium, there was no evidence of fibrin exudation or thrombosis at these sites.

The relatively thick exudation of fibrin on the capsular surface of the liver in 3 of the 4 cases was rather an odd lesion and may well have been a significant one. From any cause such a lesion is unusual and careful examination of underlying liver failed to reveal any related lesion. In one case, it is true, focal necroses were extensive but no regional correlation between the 2 lesions could be demonstrated. It should be stressed that even in the case with the longest history (11 days) this liver exudate showed no organization and was in no way different from that of the earliest case (2 days). In both, polymorphs were the only cells present and always in small numbers. Lesions in two other serous sacs were demonstrated; a fibrinous pleurisy very similar to the exudate on the liver in one case, and a diffuse mononuclear infiltration of the meninges in another.

DISCUSSION

As Coxsackie Group B virus was isolated from all 4 cases at autopsy, first and foremost one has to decide to what extent it is the aetiological agent responsible for the lesions observed. The most striking single lesion present in all cases was myocarditis in which many features corresponded with those already described by others in Coxsackie virus infections.[1-4] This observation, taken in conjunction with the fact that the virus was isolated from the myocardium of all our 4 cases, must *prima facie* be regarded as good grounds for establishing the viral aetiology of the lesion. The lesions outlined by Saphir,[14] while morphologically similar to those seen in our cases, have no viral studies to support his view of their aetiology. Stoeber's[13] cases of myocarditis in infants cannot be compared with ours as she, too, had no viral studies to prove the aetiology. Further, both the clinical picture and epidemiology differ and only 3 died in the first month of life. Most of her cases died in the stage of myocardial fibrosis around 8 months, and while we have demonstrated that scarring occurs in the Coxsackie myocarditis with unusual rapidity, the long duration of the disease would seem to suggest a different aetiological factor. It should be admitted, however, that Stoeber correlated death in her cases with physical exercise and not with the activity of the disease process. If, on the other hand, her cases were caused by the Coxsackie virus, it is surprising there was no associated epidemic of Bornholm disease.

In all 4 cases at least one fair-sized section from the myocardium failed to demonstrate any signs of myocarditis, but in no case did a section from the left ventricle fail to provide evidence of myocarditis, though sometimes to an unimpressive degree. Multiple sections, however, clearly showed that every chamber in every case was extensively involved. Nevertheless, it is clear that a single block of myocardium may fail to demonstrate the lesion.

The morphology of the myocarditis in our infants (I, VI) who died within a week after the onset of symptoms, corresponded closely with that already described in the literature.[1—4, 16, 17] The cardinal features are diffuse oedema, necrosis of the myocardial fibres and varying degrees of acute inflammatory response confined mostly to the necrotic foci. However, in the infants (VII, IV) who died 9 and 11 days respectively after the onset of the illness changes which are less frequently reported became manifest. These were characterized by loss of necrotic fibres, infiltration of histiocytes, plasma cells and lymphocytes, and proliferation of fibroblasts with early formation of collagen. This final appearance was predominantly that of fibroblastic repair and, except for the rather florid accompanying inflammatory exudate, in

many ways resembled that seen in ischaemic necrosis with fibrosis. A tendency in recent years has been to regard Fiedler's myocarditis not as a single entity, but as a morphological picture probably produced by varied and unrelated conditions. It is unlikely, however, that many cases of Coxsackie myocarditis in the past have been grouped as such, because few of them correspond to any of the phases of Fiedler's myocarditis.

Saphir *et al.*[17] state that the lesions are probably the result of intra-uterine infection, as the microscopic appearances of the myocarditis indicate a longer duration than the age of the patients. However, the rapidity of the repair processes in our cases was such that we cannot agree with the validity of this inference. Some of our cases showed a similar morphology and yet the disease had been demonstrated to have been contracted in the nursery.

A practical consideration that arises is to what extent the scarring, acquired as a result of such a lesion, will be visible in later life and what effect this will have on the functional reserve of the heart. If one keeps in mind the fact that heart weight increases from 20 grammes in the infant to 300 grammes in the adult and considers the capacity of the myocardial fibres for hypertrophy, it is doubtful if such a healed lesion, extensive as it may be in the infant, will be at all manifest in the adult, at least morphologically. For similar reasons, the functional impairment should become less evident with growth of the child. It is well documented that in the myocarditis of infective origin, the patient who recovers is left with no residual impairment of cardiac function. This, too, is supported by the cases of this series who recovered: the electrocardiograms of these have all returned to normal.

The age distribution of Coxsackie myocarditis is of some interest. Because the lesion has been reported only in infants of the neonatal period, can it be assumed that Coxsackie myocarditis does not occur in the adult? Thus far the answer, based entirely on clinical evidence, must be in the negative. The nearest approach to myocardial involvement in the adult are case reports of Coxsackie infection with evidence of pericarditis and doubtful myocarditis[5, 18] based only on clinical evidence. Weinstein[12] and Finn[15] describe cases of Coxsackie pericarditis and Bing[16] reports 6 cases of 'epidemic pericarditis' who had Bornholm disease. However, Spain *et al.*[6] in poliomyelitis cases that came to autopsy found histologically demonstrable myocarditis in 12 out of 14, although only one of these had clinical and electrocardiographic evidence of it. Similarly Ludden and Edwards[7] found evidence of associated myocarditis in 14 of 35 fatal cases of poliomyelitis. So it may be that, while Coxsackie myocarditis exists in the adult, it is subclinical and, as the patients do not die, has not been described histologically. The findings of adult patients dying of some incidental cause, whilst in the acute or convalescent stage of Bornholm disease, would thus be of interest.

In our opinion a fibrinous exudate of the peritoneal surface investing the liver, forms the second commonest manifestation of Coxsackie virus infection in the neonate. In the first of our series of cases this lesion was observed and when subsequently sought for, could be demonstrated in 2 of 3 cases. Thus 3 of our 4 cases showed this lesion. In none of the 9 cases quoted in the literature has this lesion been reported, but we feel that this may be no indication of its prevalence. Such a lesion even in the most carefully conducted autopsy could easily be missed if not specifically sought for.

The localization of the fibrinous exudate at this site is difficult to account for. In one case it was present on the anterior surface of the liver and in 2 cases on the inferior surface. If trauma were the conditioning factor, this distribution would not be expected as the inferior surface is the most protected by the cushioning effect of the bowels and the anterior surface the most prone to trauma.

A lesion of the underlying liver tissue is another likely cause to be excluded. In one case there was this association but in the 2 others no liver lesion whatever could be demonstrated. Thus, whereas we were unable to satisfactorily correlate the peritoneal exudate with morphological signs of the underlying liver, the possibility that a local concentration of virus existed in these cases in the liver was not excluded. Our virus studies on the liver are incomplete and so give us no indication of the infectiveness of these tissues but, on morphological grounds, we would go so far as to suggest that liver puncture might be tried as a means of isolating the virus in this sort of case. A further possibility is that the virus has a specific affinity for serous membranes. In our series this is supported by finding in addition a fibrinous pleurisy in one case.

In the neonate this manifestation is overshadowed by the myocarditis, but it may have an interesting bearing on adult symptomatology. In 'epidemic pleurodynia', the presence of pleurisy is well known, and in view of the

findings in our cases, it seems that the abdominal pain attributed to myalgia may be due as well to irritation of the parietal peritoneum.

The other described feature of Coxsackie infection, meningoencephalitis, was present but inconspicuous in our material. One case showed a cellular meningeal infiltrate, another slight perivascular cuffing and a third only focal microglial proliferation.

Lastly, in one case (VII) there remained a group of lesions—consisting of parotitis, focal glomerular necrosis, splenic exudation of fibrin, focal acute haemorrhages including that of the papillary muscles of myocardium and liver necrosis—which must be evaluated with regard to their viral aetiology as they have not previously been described in the cases recorded in the literature. Of these the suppurative parotitis can be dismissed as being due to secondary bacterial invasion. Similarly, the focal embolic glomerular necrosis, and the focal haemorrhages so clearly resemble secondary septicaemic manifestations as to suggest this as a possible explanation of their origin. If not due to this cause, the similarity is such that a discussion of any other pathogenesis would have very little validity. The fibrinous exudate in the spleen is difficult to explain on this basis and we leave it as an isolated observation (one out of 4 cases) for which we prefer to offer no explanation.

The focal necroses in the liver were unlike those expected in the newborn from the ordinary causes such as septicaemia. A further point against a septicaemic origin in this case were the indications of chronicity and repair, corresponding in duration to the older cardiac lesions. Neither did the appearances resemble those of hepatitis, especially the neonatal form as described by Dible *et al.*,[8] Stokes *et al.*,[9] Scott *et al.*,[10] and Smetana *et al.*,[11] in whose cases a constant finding was the presence of numerous liver giant cells. They did not resemble other forms of viral hepatitis. Although only one of the 4 cases showed these focal necroses in the liver, their appearances in an infant of this age are so unusual as to raise the question of their viral origin. It would seem advisable that all future cases of Coxsackie infection, whether in adults or infants, should be specifically investigated for the presence of hepatitis.

The liver lesions associated with Coxsackie myocarditis and described by other authors[4, 14] as hepatitis range from small collections of inflammatory cells to central necrosis of the liver lobule. We feel these lesions are non-specific and insufficient to establish the diagnosis of hepatitis on morphological grounds. The lesion we described is a full-blown, florid hepatitis with extensive necrosis, and local reactive responses on the part of connective tissue and liver parenchyma. As pointed out by Saphir *et al.*,[17] the association of myocarditis and infective hepatitis in adults is well known.

SUMMARY

1. The autopsy findings on 4 cases of Coxsackie myocarditis in neonates are added to the 9 in the literature.

2. It has been possible to describe more completely the evolution of the myocardial lesions and the rapidity of repair is the most striking observation.

3. Fresh morbid anatomical findings outside the myocardium are acute fibrinous exudate on the liver (3 out of 4 cases) and extensive focal necroses in liver (one case).

OPSOMMING

1. Die lykskouing-bevindings in 4 gevalle van Coxsackie-hartspierontsteking by pasgeborenes word gevoeg by die 9 wat reeds beskryf is.

2. Dit was moontlik om die evolusie van die hartspierontstekingsletsels vollediger te beskryf, en vinnige herstel was die opvallendste waarneming.

3. Nuwe morbiede anatomiese bevindings buite die hartspier is akute fibrienagtige uitsweetvog op die lewer (3 uit 4 gevalle) en uitgebreide brandpuntontbindings in die lewer (een geval).

We should like to thank Dr. J. R. L. Forsyth for inclusion of Case IV in this series, and Prof. J. G. Thomson for his valuable criticism and advice.

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COXSACKIE VIRUS MYOCARDITIS OF THE NEWBORN

VIRUS STUDIES

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This short report records some of the observations made during investigations of the epidemics of Coxsackie virus myocarditis of the newborn referred to in companion papers in this issue. In addition to quantitative data of virus concentrations in the tissues of 4 of the fatal cases, 2 experiments are described recording the virus concentrations in the blood and tissues of infant and adult mice infected with the same virus.

The virus isolated from all the cases was Coxsackie virus, Group B, Type 3.

Source of Virus. Virus isolations were made from faecal samples from both living and dead infants and from tissues removed at autopsy. In addition, faeces from mothers in the nursing home, the nursing staff and adults in the community of Cape Town suffering from Bornholm disease were investigated.

Preparation of Material. Faeces were emulsified in nutrient broth to make an approximately 10% emulsion. In the case of the infant stools, each specimen was then well shaken with ¼ volume of ether and left overnight at 4° C. Thereafter it was centrifuged at 3,000 r.p.m. for 1 hour in a refrigerated centrifuge. The aqueous phase was collected, freed from ether by prolonged subjection to negative pressure and 100 units penicillin and 100 μg. streptomycin per ml. added.

Emulsions of adult stools were not treated with ether, but spun at 3,000 r.p.m. for 1 hour and then penicillin and streptomycin added to the supernatant fluid.

Portions of various tissues from autopsies were ground with powdered glass and suspended in nutrient broth to make a 10% emulsion. This was regarded as 10^{-1} dilution of virus. After centrifugation at 3,000 r.p.m. for 1 hour antibiotics, as before, were added to the supernatant fluid.

All material was stored at −20° C. until required.

Tissue Culture. Trypsin digests of monkey kidney were prepared according to the method of Melnick *et al.*[1] The cells were cultured in test tubes, each of which received 6×10^5 cells and 1 ml. of nutrient medium consisting of Hanks' solution with 0.5% lactalbumin hydrolysate, 5% horse serum and antibiotics to make final concentrations of 100 units of penicillin and 100 μg. of streptomycin per ml. When ready for inoculation, the medium was replaced by maintenance medium without serum.

Tissue culture tubes were inoculated with 0.1 ml. amounts of the specimen under investigation and the cells observed for 10 to 14 days for the appearance of cytopathogenic change.

Virus titrations were made by inoculating 0.1 ml. amounts of 10-fold dilutions of the various suspensions into at least 3 tubes of monkey kidney cell culture and the end points calculated by the method of Reed and Muench.[2]

Mice. Albino mice (Onderstepoort strain) bred in our laboratories were inoculated intracerebrally or intraperitoneally with 0.2 ml. of the virus suspension. Suckling mice less than 28 hours old were used routinely for isolations, but in some experiments older suckling mice and adult mice were used.

The infected carcasses were stored at −20° C. For inoculation of tissue cultures the thawed carcasses were emulsified in nutrient broth to make a 10% suspension.

Antisera. Type sera were kindly supplied by Dr. G. Dalldorf, New York.

Immune sera were also prepared from 2 of the fatal cases using infected suckling mouse carcasses as the source of the antigen. Groups of adult mice were given 6 intraperitoneal injections of 0.5 ml. of a saline suspension of virus at 5-day intervals. The mice were bled 10 days after the last injection and the serum inactivated at 56° C. for half an hour before use.

Neutralization Tests. Viruses were typed by a standard procedure using specific immune sera diluted 1 in 5 added to an equal volume of virus

suspension containing approximately 100 $TCID_{50}$. This was left at room temperature for 1 hour and the mixture then inoculated into monkey kidney cultures.

Virus isolations from tissues removed at autopsy as well as faeces were carried out in both tissue culture and in suckling mice.

RESULTS

A cytopathogenic agent for monkey kidney cells was obtained from the stools of all 9 affected infants and from post-mortem tissues of the 4 fatal cases. In addition, virus was isolated from the faeces of one clinically unaffected newborn infant in the nursing home, one nurse, 2 visitors to the home, and from 5 cases of Bornholm disease and one case of non-paralytic aseptic meningitis outside the nursing home, and occurring at about the same time.

The cytopathogenic effect in tissue culture was usually apparent between the 4th and 6th days after inoculation and was usually complete within 2 days. The time of onset of the cytopathogenic effect correlated closely with the virus concentration in the inoculum.

Newborn suckling mice usually showed tremor and weakness 3–4 days after inoculation and died within 24 hours of the onset of symptoms. Mice surviving longer had necrosis of the fat pads between the scapulae, frequently associated with foci of calcification.

Neutralization tests indicated that all the viruses isolated were the same and this was Coxsackie Group B, Type 3.

The virus concentrations in the various tissues removed at autopsy in the 4 fatal cases are recorded in Table I. In Cases VI and VII, where the virus titre was determined in more than one tissue, it was highest in the myocardium. In Case VII, where a definite hepatic lesion was noted microscopically, there was no demonstrable virus in that organ, whilst in Case VI, where there was no obvious hepatic lesion, the amount of virus detectable in the liver was considerable.

EXPERIMENTAL WORK

Two experiments were designed to determine the extent of virus multiplication in the tissues of suckling and adult mice. Some of the adult mice were pre-treated with 2 injections of cortisone. The virus used was the Coxsackie, B3, isolated from the myocardium of Case I, Baby KAI.

Experiment 1. Groups of mice aged 1, 3, 5 and 21 days were given 0.02 ml. doses of 10^2 $TCID_{50}$/ml. of Coxsackie B3 virus by the intracerebral route. Ten mice from each group were killed on the second and fifth days after inoculation. The brains of each group were pooled and the hearts were similarly treated. The virus in these pools was titrated in monkey kidney tissue culture.

Experiment 2. Fifty mice aged 21 days were each given 1.6 mg. cortisone intraperitoneally on each of 2 successive days. Four hours after the second injection the mice were given 0.03 ml. of $10^{4.8}$ $TCID_{50}$/ml. of Coxsackie B3 virus intracerebrally.

Fifty control mice aged 21 days were each given a similar injection of virus, but without the previous administration of cortisone. A further control group of 48 2-day old suckling mice was inoculated intracerebrally with the same virus suspension in 0.02 ml. amounts.

TABLE 1: VIRUS CONCENTRATIONS IN TISSUES OF 4 FATAL CASES

Case	*Duration of Illness*	*Tissue*	*Histological Lesions*	*$TCID_{50}$/ml.*
I Baby KAI	6 days	Myocardium	Acute Extensive	$10^{5.0}$
IV Baby BRI	11 days	Myocardium	Chronic Moderately extensive	$10^{3.0}$
VI Baby NOT	2 days	Myocardium	Acute Moderately extensive	$10^{8.5}$
		Pancreas	Absent	$10^{7.5}$
		Liver	Absent	$10^{7.0}$
		Spleen	Absent	$10^{5.8}$
		Brain	Absent	$10^{4.5}$
VII Baby HAE	9 days	Myocardium	Chronic Moderately extensive	$10^{4.5}$
		Pancreas	Minimal	$10^{4.3}$
		Liver	Present	0
		Brain	Absent	0

On 6 to 8 successive days after inoculation 6 mice of each group were killed with ether vapour. The hearts from each were harvested and pooled, and the blood from the 2 groups of adult mice was collected and separately pooled. Virus titrations were carried out in monkey kidney tissue culture.

RESULTS

Experiment 1. Table II records the results of virus concentrations in the pooled brains and pooled hearts of suckling and adult mice. Each animal received 0.02 ml. of a suspension containing 10^2 $TCID_{50}$/ml.

In the 1-, 3- and 5-day old suckling mice virus concentrations were generally higher in the heart than in the brain, despite the intracerebral route of inoculation. With this inoculum no virus was detectable in the hearts or brains of the 'adult' mice on the second and fifth days.

Experiment 2. In this experiment the inoculum for all mice was 0.02 ml. of a suspension containing $10^{4.8}$ $TCID_{50}$/ml. Virus multiplication reached the highest titres in the hearts of suckling mice. It occurred earlier in the cortisone-treated adult mice than in the untreated adult animals. The pooled samples of blood from the adult mice showed in both groups a short-lived viraemia which was more obvious and appeared earlier in the cortisone-treated mice. In the pooled hearts of these 2 groups there was some evidence of virus multiplication even during the viraemic stage, but there were clear indications of persistence of virus in the heart muscle after the disappearance of the virus from the blood. Though the presence of the cortisone appeared to favour early appearance of high concentration of virus in the heart muscle, it did not result in titres higher than those ultimately encountered in the untreated animals (Table III).

DISCUSSION

Few outbreaks of Coxsackie myocarditis of the newborn have been reported. In some the virus has been demonstrated in the myocardium, but in none have quantitative studies been described.

In the 4 fatal cases recorded in this journal the virus titres in the myocardium varied from 10^3 to $10^{8.5}$ $TCID_{50}$/ml./gm. of tissue. In the 2 cases in which several organs were examined, the virus titre was highest in the myocardium. There appeared to be a clear relationship between virus concentration, the duration of the illness and the acuteness of the lesion. Thus, in Case VI (Baby NOT) the infant was ill for 2 days only, the myocardial lesion was acute and moderately extensive and the virus titre was exceptionally high, in fact the highest obtained ($10^{8.5}$ $TCID_{50}$/ml.). At the other extreme, Case IV (Baby BRI) was ill for 11 days, the myocardial lesion was moderately extensive but chronic and showing repair whilst the virus titre was low ($10^{3.0}$ $TCID_{50}$/ml.). This would indicate that the virus is present in large amounts early in the disease and gradually disappears. This probably also explains the failure to demonstrate virus in the liver despite the pre-

TABLE II: VIRUS CONCENTRATIONS IN HEARTS AND BRAINS OF MICE FOLLOWING INTRACEREBRAL INOCULATION OF COXSACKIE B3 VIRUS

Time of Harvesting after Inoculation	1-*day Old*		2-*day Old*		5-*day Old*		21-*day Old*	
	Heart	*Brain*	*Heart*	*Brain*	*Heart*	*Brain*	*Heart*	*Brain*
2nd day	$10^{4.3}$	$10^{2.8}$	$10^{4.3}$	$10^{3.5}$	$10^{3.5}$	$10^{2.5}$	0	0
5th day	$10^{6.5}$	$10^{6.5}$	$10^{5.5}$	$10^{3.5}$	$10^{4.5}$	$10^{3.8}$	0	0

TABLE III: VIRUS CONCENTRATIONS IN BLOOD AND HEART IN SUCKLING MICE, CORTISONE-TREATED ADULT MICE AND UNTREATED ADULT MICE AFTER INTRACEREBRAL INOCULATION OF COXSACKIE B3 VIRUS

Time of Harvesting after Inoculation	*Cortisone-Treated Adult Mice*		*Control Adult Mice*		*Suckling Mice*
	Heart	*Blood*	*Heart*	*Blood*	*Heart*
1st day	0	$10^{1.8}$	0	0	$10^{3.3}$
2nd day	$10^{3.5}$	$10^{4.5}$	0	0	$10^{5.5}$
3rd day	$10^{4.5}$	$10^{4.8}$	$10^{3.5}$	$10^{3.5}$	$10^{7.5}$
4th day	$10^{5.5}$	$10^{3.5}$	$10^{2.23}$	0	$10^{6.8}$
5th day	$10^{5.3}$	0	$10^{4.5}$	0	$10^{6.5}$
6th day	$10^{3.5}$	0	$10^{3.8}$	0	$10^{5.8}$
7th day	$10^{2.7}$	0	$10^{5.5}$	0	
8th day	less than 10^2	0	$10^{5.3}$	0	

sence of hepatic lesions in the Case VII (Baby HAE) who had been ill for 9 days. More difficult, however, is Case VI (Baby NOT), with abundant virus in the liver, yet no demonstrable lesion. It is possible that some of the virus here may have been due to viraemia.

Whilst virus multiplication is not confined to the myocardium, the results emphasize the importance of multiplication in this site in the pathogenesis of the disease. The striking myocardial lesion in the newborn infant seems to be a feature of the very young infant infected with Coxsackie B3 or B4 viruses, for it has not been described in older children, adolescents or adults. This correlation with age is well recognized in the difference in susceptibility of very young suckling mice compared with that in older mice.

In an attempt to find an explanation for this apparent increased susceptibility of the myocardium of newborn infants, 2 experiments were designed to determine the degree of virus multiplication in mice and to observe the effect of cortisone on the virus multiplication in the myocardium of the apparently insusceptible adult mice. These experiments avoided the massive doses of cortisone and the large virus inocula used by previous workers. The virus, moreover, was introduced intracerebrally instead of intraperitoneally.

Estimation of virus concentrations at daily intervals in the blood and the hearts of groups of adult mice of comparable size revealed some interesting results. In both the cortisone-treated and untreated groups of mice there was a transient viraemia, with virus levels rising higher and lasting longer in the former than in the latter. In the pooled hearts, on the other hand, virus was demonstrated in higher titres beyond the period of viraemia in both groups of animals but, whereas the virus concentration in the hearts of the cortisone-treated animals rose sharply and then decreased after the fifth day, the virus levels in the untreated mice showed a slower step-wise increase continuing for the 8 days of the experiment and ultimately reaching concentrations equal to that in the cortisone-treated group. Comparable results were obtained in a preliminary experiment in which a larger inoculum of virus was used. None of the mice died or showed signs of illness during the 8 days of the experiment.

Kilbourne *et al.*[3] showed that Coxsackie B3 virus produced extensive and disseminated myocardial necrosis only in the cortisone-treated adult mice, although virus concentrations reached high levels in the untreated mice. They concluded that myocardial necrosis was not caused by the effect of the cortisone on virus multiplication but 'rather the result of a synergistic toxicity of cortisone and the intrinsically cardiotropic virus'.

Our own observations confirm that the virus concentrations in the hearts were not dependent upon the administration of cortisone. Since none of our mice died during the 8-day experiment, we assume that the smaller doses of cortisone we employed were without the lethal effect which Kilbourne described. On the other hand, it is possible that our strain of Coxsackie B3 virus lacked some properties possessed by other B3 strains, since it has been shown that the effects of the virus upon the myocardium may vary with the strain of Coxsackie B virus used.[3]

Why is there such a selective vulnerability of the infant in the first few days of life? There is a comparable vulnerability in suckling mice. The adrenal organ of the newborn child is disproportionately large at birth, and undergoes rapid physiological changes and diminution in size. It is reasonable to suspect that it is responsible, in part at least, for the difference in behaviour of the Coxsackie infection very early in infancy, from the effect seen even a few weeks later. Corticoids in human cord plasma show high concentrations at birth but, at the age of 2 days, they have fallen to low levels and may even be absent. Similarly, the 17-ketosteroids are at a high level on the day of birth and fall precipitously during the next 2 days, not to rise again for at least 30 days.[4]

The epidemiological information points strongly to the onset of infection during the first few days of life. Unlike infections occurring in older infants, children, adolescents and adults in whom no cases of acute myocarditis have been reported, the myocardium during the first few days of life must be regarded as very susceptible to necrosis when infected by Coxsackie B3 virus. The factor or factors which determine this state of the myocardium have not yet been elucidated.

SUMMARY

Coxsackie B3 virus was isolated from 9 newborn infants during 2 epidemics of myocarditis of the newborn occurring in one maternity home. Virus titrations on the tissues removed *post mortem* in the 4 fatal cases showed high virus concentrations in the myocardium.

Observations on quantitative measurements of virus in the myocardium in both suckling and adult mice revealed high concentrations of virus. Although minor differences were en-

countered in cortisone-treated and untreated adult mice, virus levels were not appreciably altered by the adminstration of cortisone.

OPSOMMING

Coxsackie B3-virus is verkry van 9 pasgebore suigelinge tydens 2 hartspierontsteking-epidemies in 'n enkele kraaminrigting. Virus-titrerings met weefsels wat *post mortem* van die 4 noodlottige gevalle verwyder is, het hoë virus-konsentrasies in die hartspier aangetoon.

Waarnemings van die kwantitatiewe mate van die virus in die hartspier van sowel jong as volgroeide muise het hoë konsentrasies van die virus geopenbaar. Hoewel kleiner verskille opgemerk is by volgroeide muise wat met kortisoon behandel is en ander muise wat geen sodanige behandeling gekry het nie, is die virus-peile nie noemenswaardig deur die toediening van kortisoon geaffekteer nie.

We would like to thank Dr. G. Dalldorf, New York, for kindly sending us the type specific Coxsackie sera.

We would also like to express our appreciation of the able technical assistance of Miss M. Butchart and to Miss A. Kühr for the preparation of tissue cultures.

The Virus Research Unit received additional grants from the Nkana-Kitwe and Chingola Poliomyelitis Research Funds.

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COXSACKIE VIRUS MYOCARDITIS OF THE NEWBORN

EPIDEMIOLOGICAL FEATURES

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The first evidence of the existence of Coxsackie virus infections in the Cape Town area in 1957 appeared in the form of an explosive outbreak of 6 cases of myocarditis of the newborn.

The background to this incident was provided by an unusually severe epidemic of poliomyelitis in the area starting in April 1956, and extending into June 1957. Amongst these cases was a considerable number presenting with the signs and symptoms of a non-paralytic aseptic meningitis. With a view to labelling this group of cases more accurately, provision was made, early in January 1957 to carry out virus isolations from faecal samples from this type of case. The vast majority of the viruses isolated were poliovirus Type I. The 21st isolate was found to be Coxsackie virus Type B2, and the 27th isolate, in the latter part of April, proved to be Coxsackie virus Type B3.

It was at the beginning of this month that the first epidemic of Coxsackie virus myocarditis of the newborn occurred, and from then on, extending into July, cases of Bornholm disease occurring in adults, adolescents and children appeared in a wide-spread manner in this area. The period during which these Coxsackie infections occurred relative to the more prolonged poliomyelitis epidemic is indicated in Fig. 1.

The 2 epidemics of myocarditis of the newborn occurred in the largest of 4 privately controlled maternity homes which accommodates as many parturient mothers as the other 3 together. In addition to these private institutions, the local Provincial Hospital Authority also provides 2 maternity homes for the lower income groups of the population, while a further 2 are controlled by Church organizations for similar income groups.

The Maternity Hospital. The maternity hospital concerned in these 2 epidemics, built only 18 months before, is of modern design and has accommodation for 50 mothers.

The wards are arranged on 2 separate floors and have 1, 2 or 4 beds each. The surgical theatre and the labour wards are located at one end of the upper floor, but each floor has a large nursery for 21 cots, together with a small isolation nursery. The nursing and domestic staff, both day and night, are completely separate for the 2 floors, and the theatre staff have no duties in the wards.

Mothers admitted to this home are provided with medical and obstetrical care by their family practitioners or by specialist obstetricians. The newborn babies are usually in the care of the family practitioner, unless arrangements have been made with a paediatrician.

Sick babies are removed forthwith from the general nursery and are supervised with all necessary precautions in the isolation nursery.

THE COURSE OF THE FIRST EPIDEMIC

The first incident in the sequence of events appears to be that Mrs. KAI was delivered of her child (30 March) and 3 days later developed a pyrexia and a sore throat. This relatively mild illness caused no alarm, but 5 days after the onset of her illness her baby developed a fever with a disinclination to take its feeds (7 April). This infant was immediately removed to the isolation ward, where it died 4 days later, after an illness characterized by the clinical features of myocarditis.

This incident was reported to one of us (E. D. C.) by Dr. P. Suckling, and an immediate investigation revealed that no less than 5 other infants in the upper floor nursery were pyrexial and had signs similar to those manifested by Baby KAI. Two were seriously ill and died, while the other 3 less severely affected infants recovered. The distribution of these cases in the nursery relative to the unaffected babies and to each other in shown in Fig. 2. (The clinical and other studies on these cases appear in the accompanying reports elsewhere in this issue).

Coxsackie virus Type B3 was isolated from all 6 affected infants and although faecal samples from Mrs. KAI were not examined, neutralizing antibodies to Coxsackie virus Type B3 were demonstrated in her serum in high titre (Table 1).

All members of the nursing staff and all resident mothers were closely questioned about possible recent illnesses. Only one, Nurse DAM, was found to have suffered a short pyrexial illness with a sore throat, which had commenced several days after that of Mrs. KAI, with whom she was a close contact. A single stool examination revealed no virus.

The institution was cleared of all mothers and babies, sealed and subjected to heavy formalization before being re-opened for the admission of further patients on 15 April.

THE COURSE OF THE SECOND EPIDEMIC

On 22 June a further report was made to one of us that a similar clinical case had just been observed among the newborn infants on the same floor of the same maternity hospital. This observation proved to be correct.

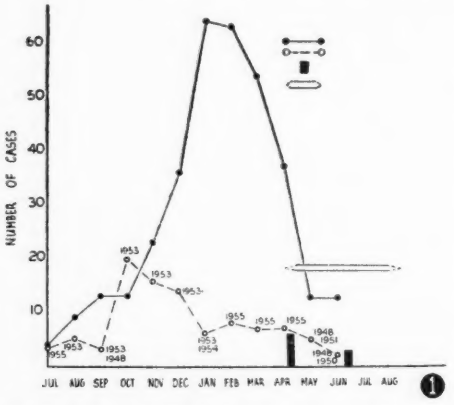


Fig. 1. The relationship between two outbreaks of Coxsackie virus myocarditis of the newborn and the poliomyelitis epidemic in the local area (1956–57).
●—● Cases of poliomyelitis 1956–57.
o– –o Cases of poliomyelitis (monthly maxima) 1948–1955.
▮ Epidemics of Coxsackie virus myocarditis of the newborn.
⊂⊃ Epidemic of Bornholm disease in the local area (approximate duration).

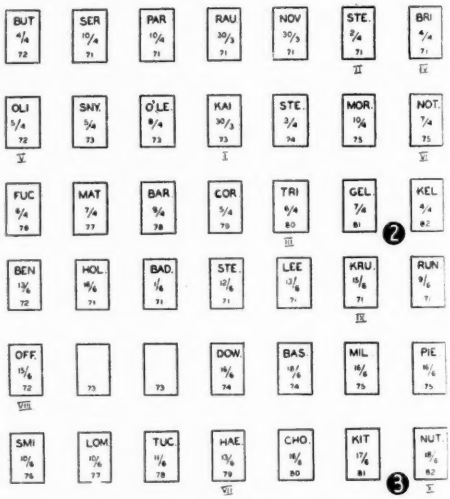


Fig. 2. Distribution of cots in the common nursery during the first outbreak of Coxsackie virus myocarditis of the newborn.
Each cot is marked with name, date of birth and number.
The 6 affected infants are marked with Roman numerals.

Fig. 3. Distribution of cots in the common nursery during the second outbreak of Coxsackie virus myocarditis of the newborn.
Each cot is marked with name, date of birth and number.
The 4 infants from whom the virus was isolated are marked with Roman numerals.

Mrs. HAE was admitted to the home late in the afternoon of 12 June and was delivered of a healthy baby the following morning. Three days later (16 June), she developed a pyrexia with headache and complained of a feeling of tightness together with muscular pains about the lower part of the chest.

Three days after Mrs. HAE became ill, her baby developed a fever with clinical signs of myocarditis and died after a stormy illness lasting 9 days. Two other infants in the same nursery became ill. One was diagnosed as a case of myocarditis of moderate severity, while the other was only mildly affected. The nursery plan in this outbreak (Fig. 3) again reveals that the secondary cases were far removed from the primary case (Baby HAE). The date of birth of each infant is also shown.

Coxsackie virus Type B3 was isolated from the faecal samples of all 3 infants and this virus was also isolated from the stool of Baby NUT, one of the nursery contacts who suffered no illness at all (Table 2).

TABLE 1: DATA ON THE FIRST OUTBREAK OF COXSACKIE VIRUS MYOCARDITIS OF THE NEWBORN

Name	*Date of Birth*	*Date of Onset of Illness*	*Virus Isolation from Stool*	*Antibodies in Serum in High Titre*	*Outcome*
Mrs. KAI		2/4	not done	+	Recovered
Baby KAI	30/3	7/4	+		Died
Baby STE	2/4	8/4	+		Recovered
Baby BRI	4/4	11/4	+		Died
Baby OLI	5/4	11/4	+		Recovered
Baby TRI	5/4	11/4	+		Recovered
Baby NOT	7/4	12/4	+		Died

EXTENT OF THE INFECTION

An attempt was made at this point to determine the extent of infection by Coxsackie Type B3 virus in the hospital. Faecal samples were collected from all the nurses, mothers and babies of the upper floor where the epidemic had occurred and, as a control group, stools were collected from 9 ground floor nursery babies. In addition, serum samples were collected from the mothers of the upper floor in order to ascertain whether any of them had antibodies to this particular virus. Included in this survey were 2 non-resident contacts who visited Mrs. HAE while she was in hospital.

Table 3 indicates that infections with Coxsackie B3 virus in the second epidemic were not confined entirely to Mrs. HAE and the 3 affected babies. The virus was isolated from Baby NUT who showed no signs of ill health at any stage, and who may be regarded as a case of subclinical infection. One of the nurses, Nurse BOO, was found to be excreting the virus. She was on duty on the upper floor during both epidemics, but in the first she mainly attended to the mothers, although she assisted in the nursery; in the second she was on night duty in the nursery only, where she nursed all the babies present at the time. During this period she was also in contact with the mothers when taking the babies to them for feeds. Two days after the second epidemic started she had an attack of 'laryngitis', but no pyrexial illness. As soon as the report on her stool was known, she was removed from duty and remained away from work until 2 negative reports had been received.

As is common practice in this type of institution, Mrs. HAE was visited in her ward by ambulant mothers, but there were no cases of

TABLE 2: DATA ON THE SECOND OUTBREAK OF COXSACKIE VIRUS MYOCARDITIS OF THE NEWBORN

Name	*Date of Birth*	*Date of Onset of Illness*	*Virus Isolation from stool*	*Antibodies in Serum in High Titre*	*Outcome*
Mrs. HAE		16/6	+	+	Recovered
Baby HAE	13/6	19/6	+		Died
Baby OFF	15/6	22/6	+		Recovered
Baby KLU	15/6	22/6	+		Recovered
Baby NUT	18/6	—	+		Unaffected

TABLE 3: ISOLATION OF COXSACKIE VIRUS TYPE B3 IN THE HOSPITAL

Designation	*Number of specimens*	*Name*	*Virus in Stool*
Groundfloor babies	9		—
Upperfloor mothers	17		—
	1	Mrs. HAE	+
Upperfloor babies	15		—
	1	Baby HAE	+
	1	Baby OFF	+
	1	Baby KLU	+
	1	Baby NUT	+
Upperfloor nurses	6		—
	1	Nurse BOO	+
Visitors (Contacts)	1	Mr. HAE	+
	1	Miss HAN	+
TOTAL	55		8

Bornholm disease among them and Coxsackie virus was not isolated from their faecal specimens.

Of the non-resident visitors to Mrs. HAE, the husband, Mr. HAE, and a family friend, Miss HAN, developed typical attacks of Bornholm disease 2 days after the onset of Mrs. HAE's illness. Besides visiting Mrs. HAE in hospital, they had both been close contacts before her admission.

One further case requires special mention. Mrs. NUT and her baby were perfectly well during their entire stay in hospital. Baby NUT, however, proved to have a subclinical intestinal infection with Coxsackie B3 virus. When the hospital was closed, Mrs. NUT returned home where, within a few days, she developed a typical attack of Bornholm disease, followed by the appearance of specific neutralizing antibodies in her serum. She was the only mother (other than Mrs. KAI and Mrs. HAE) to develop the disease and it is suggested that she acquired the infection from her baby.

Neutralizing antibodies in significant titre were demonstrable in 7 of the 48 sera examined (Table 4). These 7 sera were derived from the 3 mothers and the 4 adults known to have had Bornholm disease, and the responsible virus was isolated from the faeces of all but that of Mrs. NUT, whose stool was not examined.

Seventeen sera of the other upper-floor mothers and 23 sera sent for routine Wassermann tests were all negative. One routine Wassermann serum had a titre of less than 2.

Persistence of the Virus in the Faecal Samples. The opportunity to study more than a single faecal sample arose in 7 of those found to be excreting the virus (Table 5).

TABLE 5: PERSISTENCE OF COXSACKIE VIRUS TYPE B3 IN THE FAECES

Name	*First Specimen*	*Second Specimen*	*Third Specimen*
Baby NUT	+	—ve 15th day	
Baby KLU	+	—ve 21st day	
Baby OFF	+	—ve 24th day	
Mrs. HAE	+	+ve 13th day	—ve 39th day
Nurse BOO	+	+ve 16th day	—ve 32nd day
Mr. HAE	+	—ve 13th day	
Miss HAN	+	—ve 17th day	

It will be seen in Table 5 that although 2 individuals, only one of whom was ill, continued to excrete the virus for 13 and 16 days respectively, the virus could not be detected in the faeces of the other 5 at the second examination carried out between the 13th and 24th days.

No further investigations were carried out to determine whether this cessation was permanent or only temporary.

Evidence of Coxsackie Infections in the Community. Since Bornholm disease is not notifiable in this area, there are no available data on the incidence of cases occurring during

TABLE 4: RESULTS OF TITRATION OF NEUTRALIZING ANTIBODIES TO COXSACKIE VIRUS TYPE B3

Name	*Description*	*Titre of Antibody to Coxsackie B3 Virus*	*Number of Weeks after Onset of Illness*
Mrs. KAI	Mother of Baby KAI	48	6
Mrs. HAE	Mother of Baby HAE	24	3
Mrs. HAE	Mother of Baby HAE	64	13
Mrs. NUT	Mother of Baby NUT	24	±5
Mr. HAE	Family contact of Mrs. HAE	48	11
Miss HAN	Family contact of Mrs. HAE	64	10
Dr. WAT	Case of Bornholm disease	16	3
Mr. HAR	Case of Bornholm disease	64	2
	17 upperfloor mothers	0	
	23 Routine W. R. sera	0	
	1 Routine W.R. serum	<2	

the months April-June 1957. Few of these cases were admitted to any of the hospitals for whom we provide a laboratory service, so colleagues in private practice were invited to send us faecal samples from patients in whom a clinical diagnosis had been made. From the faeces of 9 clinical cases of Bornholm disease, Coxsackie B3 virus was isolated from 5 of them, and no virus from the remaining 4. One of the positive stools was from a young pathologist working in our laboratory and this we have preferred to regard as a case of laboratory infection.

DISCUSSION

Based on the epidemiological information presented in this report, these 2 outbreaks of Coxsackie virus myocarditis of the newborn appear to be circumscribed events in a much more wide-spread epidemic of Coxsackie virus infections in the general community.

It would appear that the 2 incidents are quite separate and distinct. The first started on 7 April and was brought to an end with the closure of the hospital on 12 April. The hospital was re-opened 3 days later without any further cases appearing until 2 months later, on 19 June.

The fact that both epidemics had occurred on the upper floor of only one of the 8 maternity institutions in this City seemed to suggest an intrinsic origin for the outbreaks. Some support for this suggestion was forthcoming when, during the second epidemic, one of the nurses (Nurse BOO) was found to be a healthy carrier of Coxsackie B3 virus, which was responsible for all the infant deaths. This nurse had attended the babies and had cared for, visited or come into contact with the 2 affected mothers, Mrs. KAI and Mrs. HAE. It seems possible that she could have been infected during or before the first epidemic and may have been the source of infection for the second if not for both outbreaks.

Such a supposition, however, appears unlikely for the following reasons. During the period under review Nurse BOO must have nursed or been in contact with about 80–100 mothers and babies, and it would be unlikely for a period of 2 months to elapse before she, as the carrier of the Coxsackie virus, was successful in infecting further individuals. It would also have to be accepted that this nurse excreted virus for at least 87 days, when (from investigations carried out in these outbreaks) the longest period that virus could be recovered from the stools of 6 other cases was less than 39 days.

It therefore seems more reasonable to accept that the epidemics were exogenous in origin. Much evidence, particularly in the second outbreak, is available to support this view. Both Mrs. KAI and Mrs. HAE developed their clinical signs and symptoms on the third in-patient day, and no other clinical cases of Bornholm disease were present among the patients and staff of the institution at the relevant times. This very brief incubation period in the case of Mrs. HAE is brought into sharp focus by the even shorter incubation periods of her 2 visitors, Mr. HAE and Miss HAN, who became ill with the same disease only two days after she did. As these 2 visitors were very close home contacts of Mrs. HAE, the likelihood is that all 3 were infected outside the hospital. Mr. HAE, a confectioner by trade, was assisted by his wife until just before her confinement. Miss HAN is also employed in the confectionery trade. All 3 had every opportunity of coming into close contact with members of the public at a time when it was known that Coxsackie infections were wide-spread in the community.

During the 2 outbreaks, Coxsackie virus Type B3 was isolated from 14 individuals, including 10 newborn infants, one mother, one nurse and 2 visitors, and high-titre neutralizing antibodies were demonstrated in the serum of one mother, whose stool was not examined. If it can be accepted that Mrs. KAI and Mrs. HAE, as well as the 2 visitors, were infected outside the hospital, the number of infections originating inside the hospital is reduced to 10 newborn infants (one of whom was not ill) and one nurse.

The infection appears to have spread very rapidly through the nursery in both outbreaks, without a similar spread among the adults in the institution. It may be postulated either that newborn infants are more susceptible to infection, or that the conditions prevailing in the nursery, such as the nursing techniques, accounted for the extent of the infection.

The only nurse found to be infected, occasionally attended the babies in the nursery in the first epidemic, but was constantly with them during the second. On both occasions she cared for all the babies and was not limited to the care of only a particular group. A careful check on the nursery technique showed it to be sound and up to date, and no reason for the outbreak could be attributed to it. The distribution of the cots (Figs. 2 and 3) in which the infected infants were nursed was random and gave no suggestion of aerial infection from one to another.

Flies,[1] which have been shown to carry the virus, and cockroaches,[2] which have been experimentally infected and remained infected for 20 days, were conspicuous by their absence and cannot be implicated in these outbreaks.

The concept of greater susceptibility of the very young infant to Coxsackie virus myocarditis gains some support from the observation that only those infants born after the first case in each outbreak became ill or infected, since all those born before that date showed no disease and no virus was isolated from their stools, although all were nursed under the same conditions in a common nursery. It is interesting to note that the age at which the infants first became ill was 8, 6, 7, 6, 6, 5, 6, 7, 7 days respectively. The possibility of intra-uterine infection cannot be entertained in 7 of the 9 cases, as their 7 mothers showed no evidence of virus excretion or of antibody production. The incubation periods of the other 2 are so similar to the rest that it is unlikely that they were intra-uterine infections either.

Although the abandonment of the common nursery and the retention of each baby in its mother's room after the second outbreak seemed to meet with success, it must also be realized that at this time there appeared to be a reduction in the incidence of Bornholm infections in the general population. On the other hand, it may well be that the nursing techniques employed under the eagle eye of the mother differed in significant respects from those carried out in the seclusion of the common nursery. The enforcement of strict attention to hand washing and the use of separate gowns for each case would tend to result in a limitation of spread of the virus. While it is acknowledged that nursing the babies in separate wards throws an additional burden on the nursing personnel, the effort is fully justified when attempting to prevent the effects of a disease of such severity in the newborn population.

Epidemics of myocarditis have been reported before, but in relatively few instances have the causal agents been isolated. In those recently described the responsible virus has been Coxsackie B2, B3 or B4.[3-7]

These two tragic incidents bring to the fore the added dangers to the newborn infant during periods of generalized Coxsackie B infections in the community, and it is very strongly recommended that these dangers be countered by the abandonment of the common nursery in this type of institution and the care of the newborn infants in the wards with their mothers.

SUMMARY

Two explosive outbreaks of Coxsackie virus myocarditis of the newborn occurring in one maternity home in Cape Town are described. There were 4 deaths among the 10 neonatal infections, of which 9 presented as clinical cases of the disease.

Epidemiological data suggest that the 2 epidemics were tragic incidents in a wide-spread epidemic of Coxsackie virus infections in the general community. Although both incidents occurred in only one of the 8 institutions dealing with maternity cases in this area, there is evidence to suggest that the infections on each occasion were introduced by the admission of a pregnant mother during the incubation period of Bornholm disease.

It is strongly recommended that efforts to avoid such outbreaks should include the abandonment of the common nursery and the retention of the newborn infant with its mother.

OPSOMMING

Twee venynige uitbrekings van Coxsackie-virushartspierontsteking onder pasgeborenes in 'n Kaapstadse kraaminrigting word beskryf. Daar was 4 sterfgevalle onder die 10 neogeboorteinfeksies, waarvan 9 hulle as kliniese gevalle van die siekte voorgedoen het.

Epidemiologiese gegewens wek die indruk dat die 2 epidemies tragiese voorvalle in 'n wydverspreide epidemie van Coxsackie-virus-infeksies onder die algemene publiek was. Hoewel albei voorvalle voorgekom het in slegs een van die 8 inrigtings waar kraamgevalle in hierdie gebied behandel word, is daar bewyse wat die mening sterk dat die infeksies in albei gevalle ingevoer is deur die toelating van 'n swanger moeder tydens die ontkiemingstydperk van Bornholm se siekte.

Daar word ten sterkste aanbeveel dat die pogings om sulke uitbrekings te voorkom onder meer die afskaffing van die gemeenskaplike kinderkamer moet insluit, en dat die pasgebore suigeling by sy moeder moet bly.

We would like to record our appreciation of technical assistance by Miss B. Robinson and Miss E. Kühr.

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NOTES AND NEWS : BERIGTE

Prof. E. B. Adams B.Sc. (S.A. *et* Oxon.), M.B., Ch.B. (Wits.), M.R.C.P. (London), Professor of Medicine at the University of Natal, has been elected a Fellow of the Royal College of Physicians, London.

* * *

NUTRITION SOCIETY OF GREAT BRITAIN

The Scottish Group of the Nutrition Society will hold a symposium on *Nutritional Hazards caused by Radioactive Contamination of Foods* in Edinburgh on Saturday, 27 September.

* * *

Medical Distributors (Pty.) Ltd., of Johannesburg, have moved into modern and spacious premises at 252 Jeppe Street where they occupy half of the first floor of 'CAPE-YORK,' an imposing new building extending from Gold to Nugget Streets.

The entrance is on the ground floor (third shop from the corner of Gold Street). An attractive staircase, the walls of which are decorated with Art Work by Ernest Ullmann, depicting scenes from Medical History, takes the visitor up to the modern showroom and offices.

All old and new friends of the firm are cordially invited to inspect the new premises. Parking for visitors will be available in the basement as soon as the building is completed. In the meantime Medical Distributors ask their visitors to press the 'Parking Button' in the Entrance, so that their cars may be parked safely.

The Johannesburg headquarters are under the personal supervision of Mr. H. J. Kretschmer, who has been connected with the medical and surgical trade in South Africa for over 20 years.

The Cape Town Agency of *Dismed* is in the hands of Mr. H. E. Lewy, 216–217 Boston House, Strand Street, who is well known to all practitioners in the Cape Province.

* * *

EXPERIMENTAL RESEARCH INTO PROBLEMS OF AGEING

The Trustees of the Ciba Foundation for the Promotion of International Co-operation in Medical and Chemical Research, 41 Portland Place, London, W.1, wishing to encourage well-conceived research relevant to basic problems of ageing, invite candidates to submit papers descriptive of work in the field for *the fifth and final annual*

AWARDS FOR 1959

Copies of the Regulations and Form of Application must be obtained from the undersigned before an entry is submitted, but in general candidates should note:

(*a*) Not less than 5 awards, of an average value of £300 each, are available for 1959. The announcement of awards will be made in August 1959.

(*b*) Entries must be received by the undersigned not later than 10 January 1959.

(*c*) Entries will be judged by an international panel of distinguished scientists including: Prof. C. H. Best (*Toronto*), Prof. E. Braun-Menendez (*Buenos Aires*), Prof. E. J. Conway (*Dublin*), Prof. G. W. Corner (*New York*), Prof. A. Haddow (*London*), Prof. V. R. Khanolkar (*Bombay*), Prof. R. Nicolaysen (*Oslo*), Dr. A. S. Parkes (*London*), Prof. F. Verzár (*Basle*), and Prof. F. G. Young (*Cambridge*). They will advise the Executive Council of the Foundation on their findings and will also have power to recommend variation in the size and number of the awards according to the standard of entries. The decisions of the Executive Council will be final.

(*d*) In making the awards preference will be given to younger workers.

(*e*) The papers may be in the candidate's own language. Papers should not be more than 7,000 words in length and in all cases a summary in English not exceeding in words 3% of the length of the paper must be attached. If possible, 10 copies of reprints in English should be provided.

(*f*) Where there is one or more co-author, the name of the leading author should be indicated; it is to him that the award will normally be made, and it will be left to his discretion to share this award appropriately with his co-authors.

G. E. W. Wolstenholme,
Director, and Secretary to the Executive Council.

PREPARATIONS AND APPLIANCES

METICORTELONE SOLUBLE

FOR INTRAVENOUS OR INTRAMUSCULAR USE

Meticortelone Soluble is prednisolone sodium hemisuccinate with phosphate buffers supplied as a dry, lyophilized sterile powder. Each 5 c.c. vial contains the equivalent of 50 mg. prednisolone.

Meticortelone Soluble produces rapid and intense hormonal effects in the crisis of acute adrenocortical insufficiency. Intensive therapy in severe infections, such as pneumonia, meningitis, etc. may permit survival time until appropriate antibiotic therapy has time to take effect. *Meticortelone Soluble* may lead to haemodynamic restoration in selected post-operative shock cases that have not responded to standard therapy and where an element of acute adrenocortical insufficiency is present or suspected.



Meticortelone Soluble Sterile Powder is intended for intravenous administration and is indicated for emergency use in conditions or situations where a rapid and intense hormonal effect is necessary or desirable. Thus the rapid intravenous injection of *Meticortelone Soluble* may be indicated in the crisis of acute adrenocortical insufficiency, bilateral adrenalectomy, post-operative shock states and in the crisis of Addison's disease or Simmonds' disease.

Meticortelone Soluble Sterile Powder may be administered intravenously or

intramuscularly. In emergency use the intravenous route is preferred. Solutions for intravenous injection are prepared by dissolving the contents of one vial *Meticortelone Soluble* in 2 c.c. sterile water for injection USP, or 2 c.c. normal saline solution sterile.

Meticortelone Soluble Sterile Powder may also be given by intravenous drip method using normal saline, distilled water or glucose solutions as the vehicle, the usual dose being 100 mg. once or twice daily.

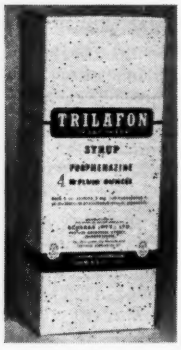
Packing: Meticortelone Soluble Sterile Powder, 50 mg. per vial, box of 1.

Scherag (Pty.) Limited, P.O. Box 7539, Johannesburg.

SYRUP TRILAFON (PERPHENAZINE)

TRANQUILLIZING AND ANTI-EMETIC

Syrup Trilafon is a powerful and highly effective tranquillizing and anti-emetic drug. In paediatric medicine it has been particularly valuable in controlling the hyperactive, emotionally or mentally disturbed child. By reducing manifestations of anxiety, hostility, tension and aggressiveness, *Trilafon* markedly improves behaviour and facilities psychotherapy or guidance. Its use is suggested in the management of assaultive, anti-social behaviour; chronic restlessness; hyperkinesia; and neurotic defence mechanisms.



Trilafon is an extremely potent anti-emetic drug and is recommended for the management of nausea and vomiting due to various causes, e.g. hyperemesis gravidarum, simple nausea and vomiting due to pregnancy, gastro-enteritis, post-operative states, carcinomatosis, radiation therapy, drug-induced vomiting, and nausea or vomiting of psychogenic origin. Average dosage range for anti-emetic effect is 8 to 16 mg. daily in divided dosage.

Dosage in Children: Children between the ages of 1 to 6 years can be started on 2 mg. 2 to 3 times daily. Children between the ages of 6 to 12 years can be started on 2 mg. 3 to 4 times daily. A total daily dose of more than 12 mg. is seldom required to elicit a favourable response.

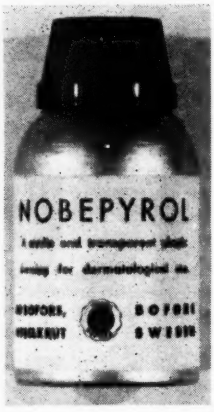
Packing: Bottles of 4 oz. and 16 oz. Each 5 c.c. contains 2 mg. of *Trilafon*.

Scherag (Pty.) Limited, Posbus 7539, Johannesburg.

NOBEPYROL

A LIQUID, PLASTIC, SPRAY-ON DRESSING FOR TAR THERAPY

Westdene Products (Pty.) Ltd. have pleasure in announcing the introduction of this new product from Bofors, Sweden. *Nobepyrol* is a liquid plastic spray-on dressing for convenient non-soiling tar therapy. It is a natural companion product to *Nobecutane*, the plastic spray-on wound dressing which has proved so successful both here and overseas.



Nobepyrol is a solution of coal tar presented in the form of a spray. When applied to skin surfaces it creates a transparent plastic film which is strong, elastic, permeable and washable. The addition of TMTD makes the solution sterile and gives the film bactericidal and fungicidal properties. *Nobepyrol* presents tar, an effective treatment for many skin conditions, in a convenient form without the disadvantage of the old type preparations. It can be applied where conventional dressings would be difficult to put on and, in addition, no covering dressings are necessary and clothes and bed linen are not soiled. Since the film is waterproof, it allows the patient to wash and yet it allows transpiration, so that the skin beneath it does not get soggy. It does not cause sensitization or irritation and, since it acts as a filter against ultra-violet light, it effectively prevents photosensitization.

Nobepyrol is intended for the treatment of dry dermatoses generally and particularly for conditions such as infantile eczema, varicose eczema, contact dermatitis, seborrhoeic dermatitis, psoriasis, etc. where 80–90% successful results have been obtained.

Nobepyrol is available in 3-oz. spray tins.

Further details may be obtained from the sole South African distributors: Westdene Products (Pty.) Ltd., Essanby House, Jeppe Street, Johannesburg.

SYRUP CHLOR-TRIMETON COMPOUND

COMPLEMENTARY ANTIHISTAMINIC AND DECONGESTIVE

Syrup Chlor-Trimenton Compound contains in each teaspoonful (5 c.c.) 1.25 mg. of the anti-histamine *Chlor-Trimenton* and 2.5 mg. of the vasoconstrictor phenylephrine hydrochloride.



Syrup Chlor-Trimeton Compound offers effective relief in nasal congestion due to common colds, vasomotor rhinitis, allergic rhinitis, coughs due to allergic bronchitis, bronchial asthma.

The complementary anti-allergic-decongestive action of *Syrup Chlor-Trimeton Compound* produces a decongestive effect greater than with either of its components acting alone. Nasal congestion is relieved and thus permits the patient to breathe freely once again. Nasal discharge is dried up to end the annoyance and discomfort of a 'runny' nose. Relief is prolonged to assure a good night's sleep.

Syrup Chlor-Trimeton Compound is so safe that it can be

prescribed even for very young children. This delicious oral medication flavour overcomes all objections from young patients. For older patients who dislike nasal medication or for those who cannot take tablets this syrup is an excellent dosage form.

Dosage: *Children under 1 Year*: One-quarter to one-half teasponful every 3 or 4 hours; *1 to 3 Years:* One-half to one teaspoonful every 3 or 4 hours; *3 to 6 Years:* One to two teaspoonfuls every 3 or 4 hours.

Adults: Two teaspoonfuls every 3 or 4 hours.

Packaging: Syrup Chlor-Trimeton Compound, bottles of 4 oz. and 16 oz.

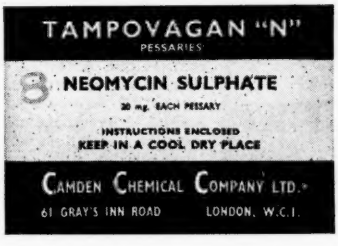
Scherag (Pty.) Limited, P.O. Box 7539, Johannesburg.

TAMPOVAGAN 'N'

FOR VAGINAL INFECTIONS

Westdene Products (Pty.) Ltd. announce the addition of a new product to their well-known range of *Tampovagan* pessaries. *Tampovagan* 'N' is a pessary containing 20 mg. neomycin sulphate in a cocoa-butter base. 'N' pessaries are intended for the treatment of vaginal infections, particularly those of mixed bacterial origin and for *Trichomonas vaginalis*. *Tampovagan* 'N' is not effective against fungi and viruses and *Pruvagol* remains the product of choice for monilia infections of the vagina.

Neomycin is the ideal antibiotic for the topical treatment of vaginal infections because it is rarely given systemically (due to possible serious toxic reactions) and has a wide range of action against a variety of gram-positive and gram-negative organisms, acid-fast bacilli and actinomycetes. It is not inactivated by pus, exudates, secretions, bacterial growth products or enzymes and is quite active in alkaline solutions. Neomycin is extremely stable at room temperature, both in dry state and in aqueous solution, and does not require refrigeration.



Directions for Use: The paper wrapper is removed and the pessary dipped into a glass of luke-warm water for one minute before insertion. One 'N' pessary is to be inserted high into the vagina every night before retiring and in the morning about 30 minutes before rising. Treatment has to be continued throughout the period of menstruation in order to prevent a recurrence of symptoms.

Tampovagan 'N' is available in boxes of 8 pessaries.

Tampovagan 'N' is manufactured by Camden Chemical Company, London, and supplies and further details may be obtained from the Sole South African Distributors, Westdene Products (Pty.) Ltd., Essanby House, Jeppe Street, Johannesburg.

ELIMIT

(BROCADES-STHEEMAN & PHARMACIA, HOLLAND)

Description: Small, flesh-coloured, sugar-coated tablets.

Composition: Each tablet contains 1 mg. reserpine and 50 mg. orphenadrine hydrochloride (*Disipal*).

Mode of Action: Reserpine acts on the autonomic and motor functions of the brain stem, and exerts a calming effect. The conduction of stimuli in the mesodiencephalic activity system is facilitated in the presence of reserpine.

Orphenadrine hydrochloride (*Disipal*), in addition to a peripheral anti-acetylcholine effect, possesses a marked atropine-like central effect with a point of action localized in the ventro-caudal area of the cerebrum. This explains the scopolamine-like activity of orphenadrine on the extrapyramidal and motor functions of the brain. Because the orphenadrine effect is predominantly central rather than peripheral, its use to influence extrapyramidal motor symptoms does not entail untoward side effects.

Indications: Specifically indicated for use in acute and chronic forms of schizophrenia, catatonic stupor, manic depressive psychoses, endogenous and reactive depressions, involutional depressions, exogenous psychoses, psychoneuroses, senile psychoses and extrapyramidal disturbances, e.g. Huntington's chorea.

Advantages: The clinical value of *Elimit* depends on its ability to make available fully effective reserpine therapy. This improved therapeutic efficiency is due to orphenadrine, which eliminates the troublesome side effects of reserpine without detracting from its desirable activity. *Elimit* has been compared, under clinical conditions in a very large number of patients, with reserpine alone and with reserpine combined with chlorpromazine. It was observed that extrapyramidal manifestations were virtually absent after *Elimit*. 'Reserpine Parkinsonism' (mask-like face, sialorrhoea, rigor, cogwheel rigidity and tremor), present in some chronic patients who had received reserpine treatment for a long time, disappeared rapidly when *Elimit* was substituted. The disagreeable effects of reserpine on the autonomic and cardiovascular systems were also markedly reduced. With the introduction of *Elimit*, fatigue, acid eructations, oedema, anorexia, bradycardia, insomnia and depression, need no longer complicate reserpine therapy in the schizophrenic.

Dosage: This should be adjusted to individual needs but generally the dosage ranges between 6–8 tablets daily.

Packing: Bottles of 100 tablets.

South African Distributors: Petersen Limited, P.O. Box 38, Cape Town, and P.O. Box 5785, Johannesburg.

ELIMITIN

(BROCADES-STHEEMAN & PHARMACIA, HOLLAND)

Description: Small, red-coloured, sugar-coated tablets.

Composition: Each tablet contains 0.2 mg. reserpine and 20 mg. orphenadrine hydrochloride (*Disipal*).

Mode of Action: Reserpine acts on the autonomic and motor functions of the brain stem, and exerts a calming effect. The conduction of stimuli in the mesodiencephalic activity system is facilitated in the presence of reserpine.

Orphenadrine hydrochloride (*Disipal*), in addition to a peripheral anti-acetylcholine effect, possesses a marked atropine-like central effect with a point of action localized in the ventro-caudal area of the cerebrum. This explains the scopolamine-like activity of orphenadrine on the extrapyramidal and motor functions of the brain. Because the orphenadrine effect is predominantly central rather than peripheral, its use to influence extrapyramidal motor symptoms does not entail untoward side effects.

Indications: All forms of minor psychic disturbances, e.g. common neurosis, psychasthenia, etc.

Advantages: The product is exceedingly well tolerated and it has been shown that the combination of these 2 substances has a more specific action on the psyche than has reserpine alone, a feature which is as important in the treatment of minor psychic disorders as it is in those cases where higher doses of reserpine are required.

Dosage: It is recommended to start treatment on 1 tablet per day; during the second week of treatment the dosage can gradually be increased to 2–3 tablets per day. After 2 to 3 weeks a maintenance dosage of 1–3 tablets is recommended.

Packing: Bottles of 30 and 100 tablets.

South African Distributors: Petersen Limited, P.O. Box 38, Cape Town, and P.O. Box 5785, Johannesburg.

PREPARATE EN TOESTELLE

METICORTELONE, OPLOSBAAR

VIR BINNE-AARSE EN BINNESPIERSE GEBRUIK

Meticortelone, Oplosbaar, is prednisoloonnatriumhemisuksinaat met fosfaatbuffers, en word beskikbaar gestel in die vorm van 'n droë, geliofiliseerde, steriele poeier. Iedere flessie van 5 k.s. bevat die gelyke van 50 mg. prednisoloon.

Meticortelone, Oplosbaar, het 'n vinnige en intense hormooneffek in die krisis van akute adrenokortikale gebrek. Intensiewe terapie tydens ernstige infeksies, soos pneumonie, harsingsvliesontsteking, ens. kan die pasiënt lank genoeg aan die lewe hou vir die geskikte antibiotica-terapie om 'n effek uit te oefen. *Meticortelone, Oplosbaar,* kan aanleiding gee tot hemodinamiese herstel in uitgesoekte na-operatiewe skokgevalle wat nie op standaard-terapie gereageer het nie, en waar 'n element van akute adrenokortikale gebrek aanwesig is of vermoed word.



Meticortelone, Oplosbaar, 'n steriele poeier, is bedoel vir binne-aarse toediening, en word aangedui vir noodgebruik in toestande of omstandighede waar 'n vinnige en intense hormooneffek noodsaaklik of wenslik is. Die vinnige binne-aarse inspuiting van *Meticortelone, Oplosbaar,* kan dus aangedui word in die krisis van akute adrenokortikale gebrek, tweesydige adrenalektomie, na-operatiewe skoktoestande, en in die krisis van Addison se siekte of Simmonds se siekte.

Meticortelone, Oplosbaar, in steriele poeiervorm, kan binne-aars of binnespiers toegedien word. In noodgevalle is die binne-aarse roete die verkieslikste. Oplossings vir binne-aarse inspuiting word voorberei deur die inhoud van een flessie *Meticortelone, Oplosbaar,* in 2 k.s. steriele water vir inspuitingsdoeleindes, USP, of in 2 k.s. normale steriele soutoplossing op te los.

Die steriele poeier, *Meticortelone, Oplosbaar,* kan ook volgens die binne-aarse drupmetode toegedien word. In sulke gevalle word gedistilleerde water of 'n glukose-oplossing as die draer gebruik, en die gewone dosis is 100 mg. een of twee maal per dag.

Verpakking: Meticortelone, Oplosbaar, 'n steriele poeier, 50 mg. per flessie, dosies bevattende 1.

Scherag (Pty.) Limited, Posbus 7539, Johannesburg.

TRILAFON-STROOP (PERFENASIEN)

'N KALMERINGS- EN BRAKINGSBESTRYDINGSMIDDEL

Trilafon-stroop is 'n kragtige en hoogs doeltreffende kalmerings- en brakingsbestrydingsmiddel. In kindergeneeskunde is dit veral waardevol vir die beheer van hiperaktiewe en emosioneel of geestelik versteurde kinders. Deur die manifestasies van besorgdheid, vyandigheid, spanning en aggressiwiteit te verminder, het *Trilafon* 'n opvallende verbeteringseffek op gedrag, waardeur psigoterapie of leiding vergemaklik word. Die gebruik daarvan word aanbeveel vir die behandeling van aanvallende, antisosiale gedrag, chroniese rusteloosheid, hiperkinesie en neurotiese verdedigingsmeganismes.



Trilafon is 'n besonder kragtige brakingsbestrydingsmiddel en word aanbeveel vir die behandeling van die mislikheid en braking wat uit verskillende oorsake voortspruit, bv. hyperemesis gravidarum, eenvoudige mislikheid en braking ten gevolge van swangerskap, maag- en dermkatar, na-operasie-toestande, karsinomatose, bestralingsterapie, die braking wat op die gebruik van geneesmiddels volg, en mislikheid en braking van 'n psigogeniese oorsprong. Die gemiddelde dosis vir die bestryding van braking is 8 tot 16 mg. per dag in verdeelde dosisse.

Dosis vir Kinders: Kinders tussen die ouderdom van 1 en 6 jaar kan begin met 2 mg. 2 of 3 maal per dag. Kinders tussen die ouderdom van 6 en 12 jaar kan begin met 2 mg. 3 tot 4 maal per dag. 'n Totale daaglikse dosis van meer as 12 mg. is selde nodig om 'n gunstige reaksie te verkry.

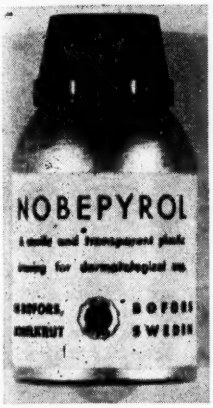
Verpakking: Bottels van 4 ons en 16 ons. Iedere 5 k.s. bevat 2 mg. Trilafon.

Scherag (Pty) Limited, Posbus 7539, Johannesburg.

NOBEPYROL

'N VLOEIBARE, PLASTIESE SPUIT-VERBINDSEL VIR TEER-TERAPIE

Westdene Products (Pty.) Ltd. kondig met genoeë die beskikbaarstelling aan van hierdie nuwe produk van Bofors, Swede. *Nobepyrol* is 'n vloeibare, plastiese spuit-verbindsel vir gerieflike nie-besoedelende teer-terapie. Dit is die natuurlike metgesel van *Nobecutane*, die plastiese spuit-verbindsel vir wonde, wat reeds met soveel sukses hier en in die buiteland gebruik word.



Nobepyrol is 'n oplossing van koolteer, aangebied in die vorm van 'n spuitmiddel. As dit aan veloppervlaktes aangewend word, vorm dit 'n deurskynende plastiese film wat sterk, elasties, deurdringbaar en wasbaar is. Die byvoeging van TMTD maak die oplossing steriel, en verleen bakterie- en swamvernietigende eienskappe aan die film. Teer, 'n doeltreffende middel vir die behandeling vir talle velkwale, word in 'n gerieflike vorm deur *Nobepyrol* beskikbaar gestel. Hierdie preparaat het geeneen van die nadele van die ouer middels nie. Dit kan aangewend word op plekke waar dit moeilik is om konvensionele verbindsels aan te lê, en daarbenewens is geen dekkingsverbande nodig om klere en bedlinne teen besoedeling te beskerm nie. Aangesien die film waterdig is, stel dit die pasiënt in staat om hom te was, en tog laat dit ook transpirasie toe, met die gevolg dat die vel onder die film nie deurweek raak nie. Dit veroorsaak geen sensitisasie of prikkelbaarheid nie, en aangesien dit as 'n filter teen ultra-violetlig optree, voorkom dit fotosensitisasie op 'n baie doeltreffende wyse.

Nobepyrol is bedoel vir die behandeling van droë dermatoses in die algemeen, en veral vir toestande soos ekseem by suigelinge, spataarekseem, kontakhuidontsteking, seborree-huidontsteking, psoriase, ens. waar tussen 80 en 90% suksesvolle resultate reeds behaal is.

Nobepyrol is verkrygbaar in spuitblikkies van 3 ons.

Nadere besonderhede is verkrygbaar van die alleenverspreiders vir Suid-Afrika, Westdene Products (Pty.) Ltd., Essanby-gebou, Jeppestraat, Johannesburg.

CHLOR-TRIMETON-STROOPSAMESTELLING

'N AANVULLENDE ANTIHISTAMIEN- EN DEKONGESTIEMIDDEL

Chlor-Trimeton-stroopsamestelling bevat, in iedere teelepelvol (5 k.s.) 1.25 mg. van die antihistamien *Chlor-Trimeton*, en 2.5 mg. van die vaatvernouer, fenielefrienhidrochloried.



Chlor - Trimeton - stroopsamestelling bied doeltreffende verligting in gevalle van neusverstopping ten gevolge van gewone verkoues, vasomotoriese neusslymvliesontsteking, allergiese neusslymvliesontsteking, en hoesbuie wat aan allergiese brongitis en brongiale asma te wyte is.

Die aanvullende anti-allergiese-dekongestiewe effek van *Chlor - Trimeton* - stroopsamestelling het 'n veel groter dekongestiewe effek as dié van die afsonderlike bestanddele. Neuskongestie word verlig, met die gevolg dat die pasiënt weer eens in staat is om vryelik asem te haal. Neusafskeidings droog op, en die oorlas en ongerief van 'n ‚lopende' neus word beëindig. Die verligting is langdurig met die gevolg dat die pasiënt 'n goeie nagrus geniet.

Chlor-Trimeton-stroopsamestelling is so veilig dat dit vir self jong kinders voorgeskryf kan word. Alle besware wat deur jong pasiënte geopper mag word, word uit die weg geruim deur die heerlike smaak van hierdie mondelinge geneesmiddel. Vir ouer pasiënte wat nie van 'n neusgeneesmiddel hou nie, of vir diegene wat nie 'n tablet kan sluk nie is hierdie stroop die ideale dosisvorm.

Dosis: *Kinders onder 1 jaar*: 'n Kwart tot 'n halwe teelepelvol al om die 3 of 4 uur; *1 tot 3 jaar*: 'n Halwe tot een teelepelvol al om die 3 of 4 uur; *3 tot 6 jaar*: Een tot twee teelepelsvol al om die 3 of 4 uur.

Volwassenes: Twee teelepelsvol al om die 3 of 4 uur.

Verpakking: *Chlor-Trimeton*-stroopsamestelling, bottels van 4 ons en 16 ons.

Scherag (Pty.) Limited, Posbus 7539, Johannesburg.

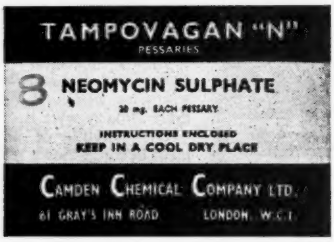
TAMPOVAGAN ‚N'

VIR INFEKSIES VAN DIE VAGINA

Westdene Products (Pty.) Ltd. kondig aan dat hul bekende reeks *Tampovagan*-steekpille met 'n verdere nuwe produk aangevul is. *Tampovagan* ‚N' is 'n steekpil wat 20 mg. neomisiensulfaat in 'n kakaobotterbasis bevat. ‚N'-steekpille is bedoel vir die behandeling van infeksies van die vagina, veral dié van 'n gemengde bakteriese oorsprong, en vir *Trichomonas vaginalis*. *Tampovagan* ‚N' is nie doeltreffend teen swamme en virusse nie, en *Pruvagol* bly die verkieslike produk vir die behandeling van monilia-infeksies van die vagina.

Neomisien is die ideale antibioticum vir die plaaslike behandeling van vagina-infeksies want, met die oog op moontlike ernstige toksiese reaksies, word dit selde sistemies toegedien. Dit het 'n breë bedrywigheidsbestek teen 'n verskeidenheid van Gram-positiewe en Gram-negatiewe organismes, basille wat teen suur bestand is, en aktinomycetes. Dit word nie onaktief gemaak deur etter, uitsweetvog, afskeidings, die produkte van bakteriese groei of ensieme nie, en is heeltemal aktief in alkaliese oplossings.

Neomisien is besonder stabiel teen kamertemperatuur, sowel in sy droë vorm as in waterige oplossings, en dit is nie nodig om dit in 'n koelkas te bêre nie.



Gebruiksaanwysings. Die papieromhulsel word afgehaal, en die steekpil word 'n minuut lank in 'n glas louwarm water gedoop voordat dit ingesteek word. Een ‚N'-steekpil moet elke aand voor slapenstyd en soggens, 30 minute voordat die pasiënt opstaan, hoog in die vagina ingesteek word. Die behandeling moet dwarsdeur die menstruasietydperk volgehou word om 'n herverskyning van die simptome te voorkom.

Tampovagan ‚N'-steekpille is verkrygbaar in dosies wat 8 bevat.

Tampovagan ‚N' word vervaardig deur die Camden Chemical Company, Londen, en voorrade en nadere inligting is verkrygbaar van die alleenverspreiders vir Suid-Afrika, Westdene Products (Pty.) Ltd., Essanby-gebou, Jeppestraat, Johannesburg.

ELIMIT

(BROCADES-STHEEMAN & PHARMACIA, HOLLAND)

Beskrywing: Klein, vleeskleurige, versuikerde tablette.

Samestelling: Iedere tablet bevat 1 mg. reserpien en 50 mg. orfenadrienhidrochloried (*Disipal*).

Werkingsmetode: Reserpien werk op die outonomiese en motoriese funksies van die breinstam in, en oefen 'n kalmerende effek uit. Die geleiding van stimuli in die aktiwiteitstelsel van die mesotussenharsings word in die aanwesigheid van reserpien vergemaklik.

Orfenadrienhidrochloried (*Disipal*) het nie alleen 'n randstandige anti-asetielcholien-uitwerking nie, maar oefen ook 'n opvallende atropien-agtige sentrale effek uit, met die inwerkingspunt gelokaliseer in die ventrokoudale gedeelte van die grootharsings. Dit verduidelik die skopolamien-agtige uitwerking van orfenadrien op die ekstra-piramidale en motoriese funksies van die brein. Omdat die orfenadrien-effek in die eerste en vernaamste plaas sentraal liewer as randstandig is, is daar geen onaangename neweeffekte as dit gebruik word om ekstra-piramidale motoriese simptome te beïnvloed nie.

Indikasies: Dit word spesifiek aangedui vir gebruik in gevalle van akute of chroniese schisofrenie, katatoniese bewusteloosheid, maniese neerslagtigheidspsigoses, endogene en reaktiewe neerslagtigheid, involusie-neerslagtigheid, eksogene psigoses, psigoneuroses, seniele psigoses en ekstra-piramidale versteurings, bv. Huntington se senuweetrekkings.

Voordele: Die kliniese waarde van *Elimit* spruit voort uit die middel se vermoë om ten volle doeltreffende reserpien-terapie beskikbaar te stel. Hierdie verbeterde terapeutiese doeltreffendheid moet toegeskryf word aan die orfenadrien, wat die lastige newe-effekte van reserpien uitskakel sonder om afbreuk aan laasgenoemde se wenslike bedrywigheid te doen. Onder kliniese toestande en by 'n baie groot aantal pasiënte is *Elimit* vergelyk met reserpien alleen, en met reserpien verenig met chlorpromasien. Daar is waargeneem dat ekstra-piramidale manifestasies byna geheel en al afwesig is na die toediening van *Elimit*. ‚Reserpien-Parkinsonisme' ('n maskeragtige gesig, speekselvloed, styfheid, kamratonbuigbaarheid en bewing) wat opgemerk is by sommige chroniese pasiënte wat oor 'n lang tydperk met reserpien behandel is, het gou-gou verdwyn toe *Elimit* die plek van die reserpien ingeneem het. Die onaangename effek van reserpien op die outonomiese en die hart-bloedvatstelsel is ook opmerklik verminder. Met die beskikbaarstelling van *Elimit* hoef uitputting, suur-windbreek, edeem, anoreksie, stadige hartslag, slaaploosheid en neerslagtigheid nie langer die behandeling van die schisofrenie-lyer met reserpien te bemoeilik nie.

Dosis: Dit behoort by individuele behoeftes aangepas te word, maar oor die algemeen is dit tussen 6 en 8 tablette per dag.

Verpakking: Bottels van 100 tablette.

Suid-Afrikaanse Verspreiders: Petersen Beperk, Posbus 38, Kaapstad, en Posbus 5785, Johannesburg.

ELIMITIN

(BROCADES-STHEEMAN & PHARMACIA, HOLLAND)

Beskrywing: Klein, rooi, versuikerde tablette.

Samestelling: Iedere tablet bevat 0.2 mg. reserpien en 20 mg. orfenadrienhidrochloried (*Disipal*).

Werkingsmetode: Reserpien werk op die outonomiese en motoriese funksies van die breinstam in, en oefen 'n kalmerende effek uit. Die geleiding van stimuli in die aktiwiteitstelsel van die mesotussenharsings word in die aanwesigheid van reserpien vergemaklik.

Orfenadrienhidrochloried (*Disipal*) het nie alleen 'n randstandige anti-asetielcholien-uitwerking nie, maar oefen ook 'n opvallende atropien-agtige sentrale effek uit, met die inwerkingspunt gelokaliseer in die ventrokoudale gedeelte van die grootharsings. Dit verduidelik die skopolamien-agtige uitwerking van orfenadrien op die ekstra-piramidale en motoriese funksies van die brein. Omdat die orfenadrien-effek in die eerste en vernaamste plaas sentraal liewer as randstandig is, is daar geen onaangename neweeffekte as dit gebruik word om ekstra-piramidale motoriese simptome te beïnvloed nie.

Indikasies: Alle vorms van ligte psigiese versteurings, bv. gewone neurose, geestesswakheid, ens.

Voordele: Die middel word buitengewoon goed verdra, en daar is aangetoon dat 'n samestelling van die twee bestanddele 'n meer spesifieke effek op die psige het as reserpien alleen—'n kenmerk wat van net soveel belang by die behandeling van ligte psigiese versteurings is as by die behandeling van gevalle wat groter dosisse reserpien vereis.

Dosis: Daar word aan die hand gedoen dat die behandeling moet begin met 1 tablet per dag. Gedurende die tweede week van behandeling kan die dosis geleidelik vermeerder word tot 2–3 tablette per dag. Na 2 of 3 weke word 'n instandhoudingsdosis van 1–3 tablette aanbeveel.

Verspakking: Bottels van 30 en 100 tablette.

Suid-Afrikaanse Verspreiders: Petersen Beperk, Posbus 38, Kaapstad, en Posbus 5785, Johannesburg.